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Case report

An experience with ibrutinib monotherapy for Richter's syndrome isolated in the central nervous system

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Richter's syndrome (RS) of the central nervous system (CNS) is known to have an extremely poor prognosis. Ibrutinib has been reported to have some activity in patients with RS, despite its poor prognosis. Although ibrutinib crosses the blood-brain barrier, its efficacy in RS patients with CNS involvement remains unknown. Here, we report a case of RS isolated in the CNS that was confirmed to be clonally related to chronic lymphocytic leukemia (CLL) by *immunoglobulin heavy chain* gene analysis. Although the median survival of patients with RS clonally related to CLL was significantly shorter than that of patients with RS clonally unrelated to CLL, the patient received ibrutinib monotherapy without experiencing any significant adverse events, and the disease remained stable with ibrutinib until 6 weeks later. Following whole-brain radiation therapy (40 Gy in 20 fractions) with dexamethasone, the patient has survived for five months after diagnosis. Thus, ibrutinib may be a safe and effective therapeutic option for patients with RS and CNS involvement.

Keywords: Ibrutinib, Richter's syndrome, Central nervous system, Immunoglobulin gene

INTRODUCTION

The prognosis of Richter's syndrome (RS) is poor,[1] and the median survival of patients with RS clonally related to chronic lymphocytic leukemia (CLL) is significantly shorter than that of patients with RS clonally unrelated to CLL.[2] Furthermore, the median survival of patients with RS exhibiting central nervous system (CNS) involvement is shorter than that of RS occurring at other sites.[3] Despite this poor disease prognosis, the Bruton's tyrosine kinase inhibitor ibrutinib has been reported to be effective in treating patients with RS,[4,5] and the blood-brain barrier permeability of ibrutinib has been recently demonstrated.[6-10] However, the efficacy of ibrutinib in patients with RS presenting with CNS involvement remains unclear.

Herein, we report a case of RS isolated in the CNS that was confirmed to be clonally related to CLL by *immunoglobulin heavy chain* (*IGH*) gene analysis. The patient received ibrutinib monotherapy without significant adverse events, and the disease remained stable with ibrutinib treatment until disease progression 6 weeks later.

CASE REPORT

A 61-year-old man was admitted to our hospital after experiencing diplopia for one month. Magnetic resonance imaging (MRI) of the brain showed high-intensity lesions on T1 weighted images with enhancement after gadolinium administration in the brain stem and parietal lobes (Figure 1a and b). Brain biopsy revealed diffuse infiltration of atypical large lymphocytes (Figure 2b). The patient was diagnosed with stage IV diffuse large B-cell lymphoma (DLBCL). Eighteen months before admission, his peripheral blood presented with small lymphocytes expressing CD5, CD19, CD20, CD22, CD23 (low), CD25 (low), and monoclonal kappa light chain, but not CD10, CD38, CD103, or FMC7. The patient presented with a normal G-banding karyotype, and fusions of *IGH* and *cyclinD1* were not detected by fluorescence *in situ* hybridization (FISH). Phenotypic evaluation of the cell populations revealed CLL (Figure 2a). Whole-body computed tomography was performed for staging following the diagnosis of DLBCL and CLL; splenomegaly was subsequently detected, but not lymphadenopathy or hepatomegaly. Bone marrow aspiration showed infiltration of the same cells as observed in the peripheral blood. CLL was evaluated as an intermediate disease based on the revised

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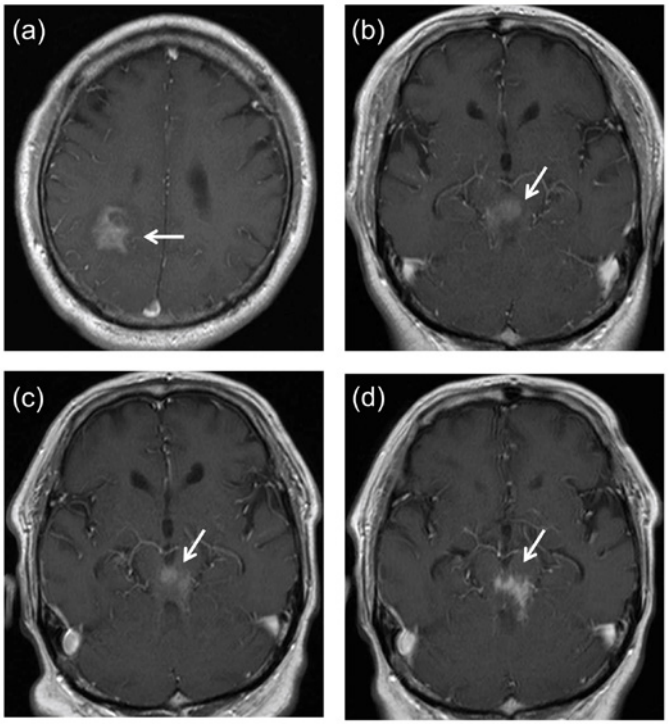

Fig. 1. Magnetic resonance imaging of the brain at initial diagnosis and after treatment: Gadolinium-enhanced T1 weighted images reveal a high-intensity lesion in the parietal lobe (***a***) and brain stem (***b***). The lesion improved after ibrutinib monotherapy (***c***). Six weeks after administration of ibrutinib, the lesion worsened (***d***).

Rai staging system, stage A based on the Binet staging system, and RS developed in the CNS following CLL. Peripheral blood showed no 11q or 17p deletions, as determined by FISH.

To clarify the clonal relationship between DLBCL in the CNS and CLL cells, we performed *IGH* gene analysis after obtaining informed consent from the patient. DNA was extracted from mononuclear cells obtained from peripheral blood and brain tumor cells. The *IGH* genes in the DNA were amplified by polymerase chain reaction (PCR) using primers for variable regions, including the heavy chain complementarity-determining region 3.[11-13] The first PCR, using primers FR2B-CFW1, and the second PCR, using primers FR2B-SJHb, were performed using a semi-nested method (Table 1). Agarose gel electrophoresis of the PCR products from peripheral blood and the brain tumor yielded the same bands under 250 bp (Figure 2c). To verify the base sequence, a cloned plasmid sequence was used. The PCR products were ligated using a vector and transformed into the plasmid DNA. Plasmid sequences showed plasmid clones with 236 base pairs from peripheral blood and the brain tumor. Twelve plasmid clones were identified in the PCR products of the peripheral blood. Three out of the 12 were original clones, and the other nine subpopulations had two-to-three additional base pairs compared to the original clones. Eleven plasmid clones were identified in the PCR products of the brain tumor; three out of the 11 were original clones, and the other eight subpopulations had one-to-six additional base

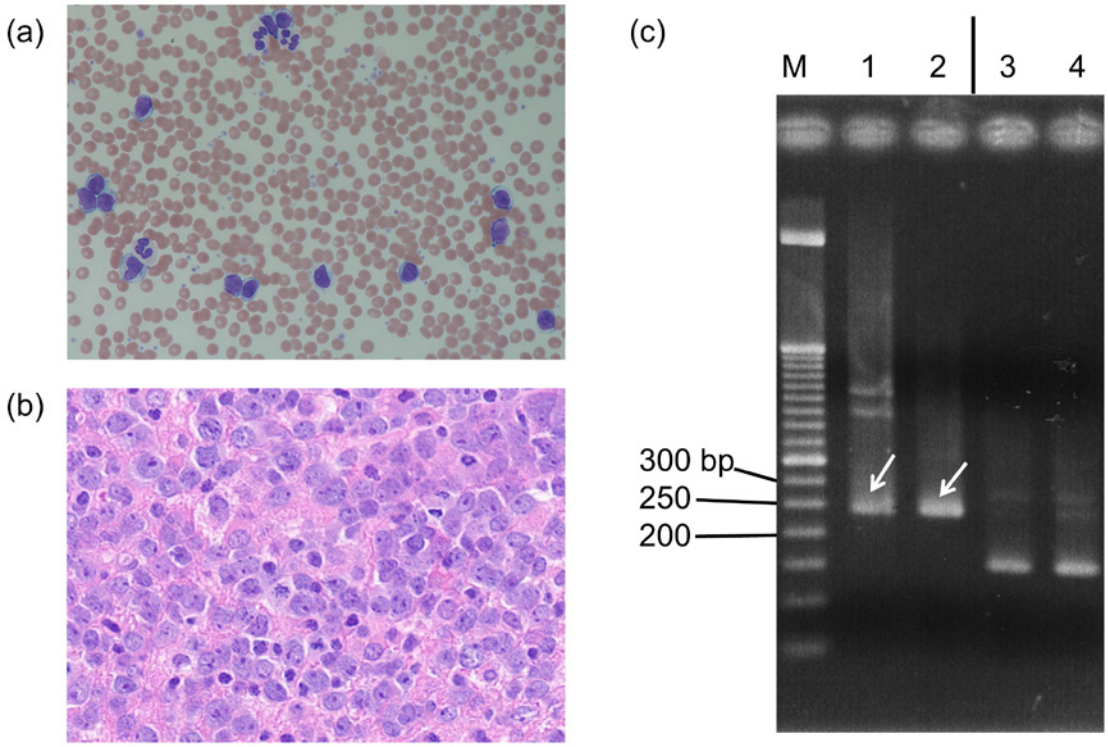

Fig. 2. May-Giemsa staining of the peripheral blood shows small lymphocytes with narrow cytoplasm (***a***). Hematoxylin and eosin staining of the brain biopsy shows atypical large-sized lymphoid cells diffusively infiltrating into the parenchyma (***b***). Polymerase chain reaction (PCR) amplified the genes of *immunoglobulin heavy chain* in lanes 1 and 2 and β-actin in lanes 3 and 4 (control) (***c***). Lanes 1 and 3 show the patient's sample DNA isolated from the mononuclear cells of the peripheral blood. Lanes 2 and 4 show DNA extracted from the brain tumor. The amplified PCR products from the peripheral blood and brain tumor were recognized at the same size of 236 (arrows).

Table 1. Sequences of immunoglobulin heavy-chain primers

FR2B	5'-GTCCTGCAGGC (C/T) (C/T) CCGG (A/G) AA (A/G) (A/G) GTCTGGAGTGG-3'
SJHb	5'-ACCAGGGTCCCTTGGCCCCA-3'
CFW1	5'-ACCTGAGGAGACGGTGACCAGGGT-3'

pairs compared to the original clones. The sequence was aligned using the ImMunoGeneTics sequence directory (http://www.imgt.org/IMGT_vquest/vquest). The common *IGH* gene rearrangement patterns of IGHV3-48*02 or 04, IGHD2-21*01, and IGHJ4*03 were identified in both peripheral blood and brain tumor clones. Thus, we confirmed that the DLBCL of the CNS develop from CLL cells.

The patient was administered 420 mg/day ibrutinib monotherapy owing to his worsened performance status. Steroids were not used in combination because of the presence of diabetes. His neurological dysfunction improved concurrent with a reduction in CNS involvement, and he achieved disease control without significant adverse events (Figure 1c). Six weeks after initiating ibrutinib treatment, the patient experienced disorientation, and MRI indicated disease progression (Figure 1d). Following whole-brain radiation therapy (40 Gy in 20 fractions) with dexamethasone, the patient has survived for five months after diagnosis.

DISCUSSION

Herein, we present a case of DLBCL of the CNS (clonally related CNS-RS) which developed from CLL cells. The patient was effectively and safely treated with ibrutinib monotherapy.

We confirmed by *IGH* gene analysis that DLBCL of the CNS developed from CLL cells. In a prior study, RS was found to be clonally related to CLL in 50 of 63 cases (79.3%) and clonally unrelated in 13 of 63 cases (20.6%).[2] Patients with clonally unrelated RS have a median survival rate of approximately 62 months; however, the median survival rate of patients with clonally related RS, as in the present case, is considerably shorter, ranging from 8-to-14 months.[2] In this case, *IGH* gene analysis revealed the clonality of RS with CLL, as well as different base pairs in the brain tumor from CLL cells. Additive mutations in brain tumors derived from peripheral CLL cells indicate that the acquisition of such mutations might lead to the development of RS. Confirmation of whether RS isolated in rare sites is clonally related to CLL is a clinically useful means for predicting the prognosis and understanding the pathology.

In the present case, a patient with RS isolated in the CNS was efficaciously and safely treated with ibrutinib. Although the prognosis of RS remains poor, especially with CNS involvement,[3] ibrutinib has been found to be an effective treatment.[4,5] Furthermore, ibrutinib is effective and safe for the treatment of primary CNS lymphoma[6-8] and mantle cell lymphoma with CNS involvement.[9,10] The permeability of ibrutinib across the blood-brain barrier was determined by measuring its concentration in the cerebrospinal fluid (CSF) of patients.[6-10] The unbound brain-to-plasma concentration ratio of ibrutinib, a pharmacokinetic parameter, was reported to be 9.8% in rats.[8] A CSF-to-plasma ibrutinib concentration ratio of 1–7% has been reported in patients.[9] Up to a certain concentration, ibrutinib can dose-dependently inhibit the proliferation of DLBCL cell lines *in vitro* and increase apoptosis in rat brain tumors.[8] Specifically, the mean CSF ibrutinib concentration was 0.77 ng/mL and 1.95 ng/mL in patients receiving 560 and 840 mg/day, respectively.[6] In our case, the patient was treated with ibrutinib at a dose of 420 mg/day, and disease control was achieved within a short period without significant adverse events. Given the safety of ibrutinib at a dose of 420 mg/day in the present case and the dose-dependent increase in CSF ibrutinib concentrations in patients receiving 560 and 840 mg/day,[6] high-dose ibrutinib therapy might be effective. The treatment strategy optimized for the disease type after transformation is the most frequently selected treatment for RS. DLBCL is the most common type of RS transformation, and chemotherapy, such as high-dose methotrexate and/or radiotherapy, is administered for RS with CNS involvement. However, these treatment strategies exhibit undesirable outcomes and are often markedly toxic to unfit patients.[3] Novel agents, such as venetoclax, have been reported to be effective against CLL; however, venetoclax was found not to cross the blood-brain barrier in a patient with RS presenting with CNS involvement.[14] Therefore, ibrutinib may be a good therapeutic option for patients with unfit RS and CNS involvement.

In conclusion, DLBCL of the CNS can develop RS from peripheral CLL cells, and this case report suggests that ibrutinib may be a safe and effective treatment for patients with RS presenting with CNS involvement despite its poor prognosis. This is important as additional therapeutic strategies are required to treat CNS-RS, which still has a poor prognosis.

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AUTHOR CONTRIBUTIONS

YN was responsible for the preparation of this manuscript. KI, KT, and KO supported the pathological evaluation and *IGH* gene analysis. YN, KN, KY, AS, TS, YK, and HM treated the patients. KN supervised the manuscript preparation.

CONFLICT OF INTEREST

None.

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