Clinical Case Report

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Occurrence of lymphoplasmacytic lymphoma in a chronic myeloid leukemia patient following long-term treatment with tyrosine kinase inhibitors

A case report

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Abstract

Introduction: After tyrosine kinase inhibitors (TKIs) targeting BCR-ABL1 were introduced for the treatment of chronic myeloid leukemia, clinical outcomes have improved dramatically. However, together with the increase in the survival rate, a more frequent occurrence of secondary malignancies has been observed as well. TKIs have been demonstrated to be a risk factor of malignancies such as non-Hodgkin lymphoma, prostate cancer, and skin cancer. However, lymphoplasmacytic lymphoma (LPL) has never been reported as a secondary malignancy after TKI treatment in chronic myeloid leukemia (CML).

Patient concerns: An 81-year-old male patient diagnosed with CML and treated with TKIs for a long period (15 years) was admitted due to a chief complaint of abdominal pain. A large abdominal mass was detected by imaging that included computed tomography.

Diagnosis: LPL was confirmed from biopsies after ultrasonography and sigmoidoscopy. Serum IgM level was increased and M protein and monoclonal gammopathy, IgM_kappa light chain type were detected.

Interventions: The patient received six cycles of R-CHOP chemotherapy.

Outcomes: After chemotherapy, he showed response. The sizes of the abdominal mass and lymph nodes decreased; moreover, serum M protein and IgM levels decreased, as well.

Conclusion: Herein, for the first time, we describe a patient who developed LPL as a secondary malignancy after administration of TKIs for the treatment of CML. Our observations indicate the importance of awareness of this secondary malignancy that can develop in CML patients treated with TKIs.

Abbreviations: CML = chronic myeloid leukemia, LPL = lymphoplasmacytic lymphoma, NHL = non-Hodgkin's lymphoma, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and methylprednisolone; TKI = tyrosine kinase inhibitor, WM = Waldenström's macroglobulinemia.

Keywords: chronic myeloid leukemia, lymphoplasmacytic lymphoma, tyrosine kinase inhibitor

1. Introduction

Chronic myeloid leukemia (CML) is one of myeloproliferative neoplasms characterized by proliferation of myeloid cells in both bone marrow and peripheral blood. It is associated with *BCR-ABL1* fusion gene that is formed as a result of translocation of chromosomes 9 and 22. Tyrosine kinase inhibitors (TKIs) bind to the kinase domain of BCR-ABL1 fusion protein and suppress its abnormal activity and downstream signaling pathways. After imatinib, a first-generation TKI, had been introduced as first-line treatment of chronic phase (CP) of CML, the 10-year overall survival (OS) increased to 83%.[1] Furthermore, the five-year OS of 94% and 91% was achieved after the second-generation TKIs nilotinib and dasatinib were approved as the first-line treatment of CML-CP.[2] Despite TKIs improved the survival rate, an increased rate of secondary malignancies in TKI-treated CML patients has been reported. In particular, TKIs have been discussed as a risk factor of secondary malignancies, such as prostate, colorectal cancer, and non-Hodgkin's lymphoma (NHL).[2,3]

Lymphoplasmacytic lymphoma (LPL) is a low-grade B-cell lymphoma characterized by immunoglobulin M (IgM) monoclonal gammopathy. These malignant cells derive from B-cell

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Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors have no conflicts of interest to disclose.

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arrest after somatic hypermutation in germinal center.[4] Increased serum level of IgM pentamer induces hyperviscosity of blood, which in turn causes vision disturbances and neurological symptoms that are observed in this disease. Rituximab-based chemotherapy regimens such as bendamustine + rituximab, bortezomib + dexamethasone + rituximab, and rituximab + cyclophosphamide + dexamethasone are preferred as initial therapy for LPL.

There have been described cases of CML that occurred in patients with Waldenström's macroglobulinemia (WM), a chlinicopathological LPL entity,[5,6] however, to the best of our knowledge, there have been no case reports yet of LPL occurrence in TKI-treated CML patients. Here, we present the first such case of a CML patient who developed LPL after administration of TKIs.

2. Case presentation

An 81-year-old man was admitted to the Department of Hematology/Oncology, because of persistent abdominal pain in September 2018. He received a diagnosis of CML-CP and started to take hydroxyurea in March 2002. From February 2003, imatinib at a daily dose of 400 mg was prescribed, because disease progression to the accelerated phase was detected by bone marrow examination. He started to take dasatinib from August 2010, because the loss of molecular response to imatinib was detected. The *BCR-ABL/ABL* ratio examined by real-time PCR had increased from 0.035688 to 0.166125. The major molecular response (MMR; IS $\leq$ 0.1%) was not obtained over 2 years, however, no additional mutations were detected. Therefore, radotinib (800 mg daily) was prescribed in November 2012. MMR (IS: 0.066%) was achieved in September 2015, and the patient developed a complete molecular response in August 2016.

When he was admitted because of a chief complaint of abdominal pain, physical examination showed a blood pressure of 125/68 mmHg, pulse rate of 75/min, respiratory rate of 18/min, and body temperature of 36.9°C. Complete blood count showed a white blood cell count of 9430/μL, hemoglobin level of 11.6 g/dL, and platelet count of 174,000/μL. To evaluate the cause of abdominal pain, a computed tomography (CT) scan was performed. A large peritoneal mass (151 × 115 mm) was found in the central part of abdomen that was adjacent to the small intestine and sigmoid colon (Fig. 1). A large infiltrative mass with central ulceration at 20 cm from the anal verge was detected by sigmoidoscopy and a tissue sample was taken (Fig. 2). Ultrasonography-guided percutaneous biopsy of abdominal mass was also performed. As a result, a diagnosis of lymphoplasmacytic lymphoma was confirmed (CD20, CD10, BCL2; positive) in both tissue samples (Fig. 3). Furthermore, ^{18}fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET-CT) was performed to determine lymphoma stage. FDG-avid mass involving small intestine and sigmoid colon was detected and multiple lymph nodes from the chest to pelvic cavity were involved (Fig. 4). There was no evidence of lymphoma infiltration in the bone marrow. Serum IgM level was increased up to 1631.0 mg/dL. M protein level of 0.99 g/dL and monoclonal gammopathy, IgM_kappa light chain type were detected by serum protein electrophoresis and immunofixation EP, respectively. As somatic mutations of *MYD88* are associated with approximately 90% of LPL/WM cases,[7] we performed next-generation sequencing of the sample from this patient. *MYD88* mutations were not detected, however, we found *TP53* p.Y236C and p.A283P mutations. The patient received chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and methylprednisolone).[8]

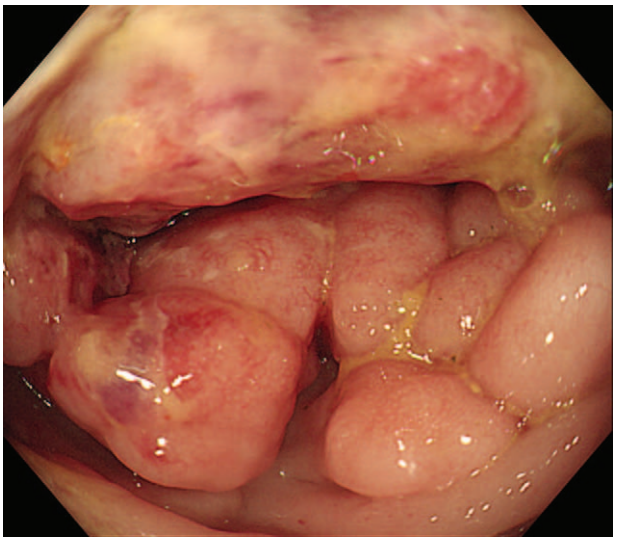

Figure 2. A large infiltrative mass with central ulceration at 20 cm from anal verge was detected by sigmoidoscopy.

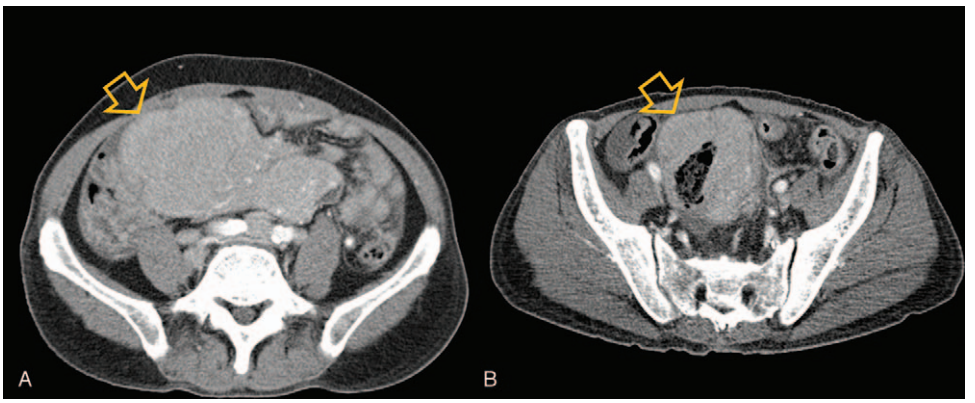

Figure 1. Abdominopelvic CT scan shows that large peritoneal mass (151 × 115 mm) decreased (79 × 74 mm) after 6 cycles of R-CHOP chemotherapy.

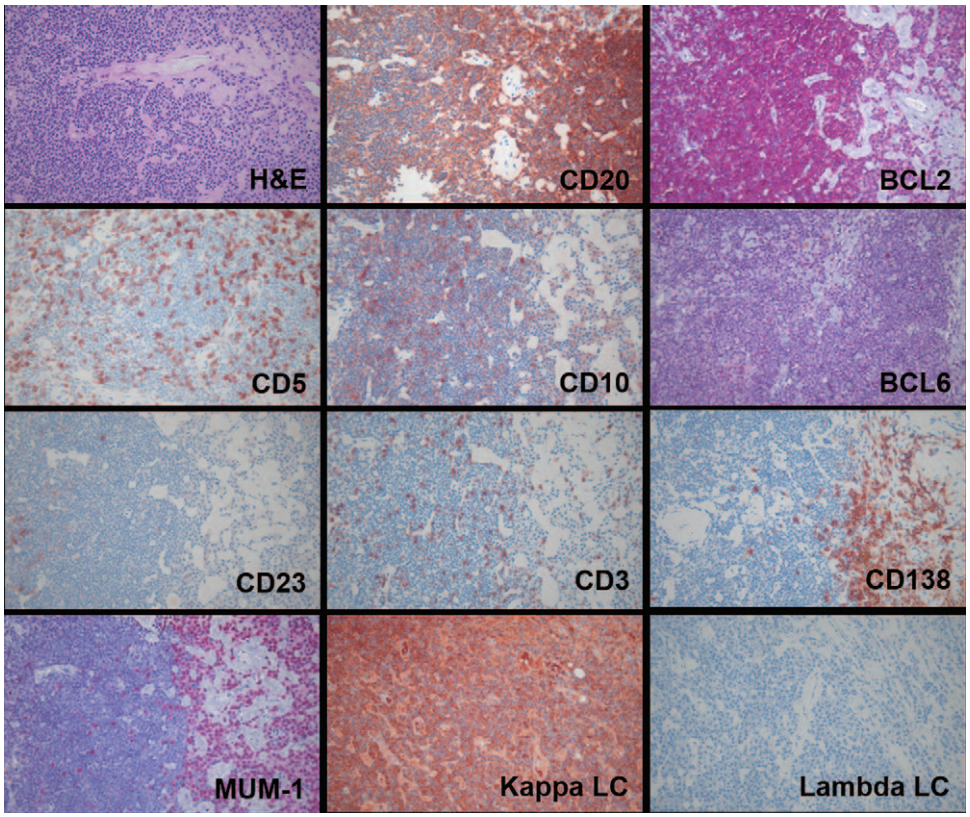

Figure 3. Histologic findings of lymphoplasmacytic lymphoma. The tumor composes of monotonous small lymphocytes and plasma cells. The small B lymphocytes are positive for CD20 and BCL2, but negative for CD5, CD10, BCL6, CD23, and CD3. The plasma cells are positive for CD138 and MUM-1, and shows kappa immunoglobulin light-chain restriction: positive for kappa light chain but negative for lambda light chain. Original magnification: ×400.

Separate CT and ^{18}F-FDG PET/CT scans followed after six cycles of the chemotherapy. The sizes of the abdominal mass and lymph nodes decreased on both CT and ^{18}F-FDG PET-CT scan images (Figs. 1 and 4). Serum M protein and IgM levels decreased to 0.13 g/dL and 280.2 mg/dL, respectively. The duration of follow-up is 17 years after he was diagnosed with CML and 6 months after diagnosed with LPL.

3. Discussion

Constitutional activation of *BCR/ABL1* tyrosine kinase is induced by the translocation of chromosomes 9 and 22, yielding t(9;22)(q34;q11). The unusually short chromosome 22 containing *BCR/ABL1* fusion gene is called Philadelphia chromosome. TKIs are competitive inhibitors of ABL protein tyrosine kinase that block ATP binding site.[9–11] After TKIs were prescribed for CML-CP patients as first-line treatment, the survival rate dramatically improved. The percentage of patients with 10-year OS after imatinib administration was 83%, whereas 91% and 94% had five-year OS after the treatment with nilotinib and dasatinib, respectively.[1]

Despite the outstanding therapeutic efficacy of TKIs, there are some adverse effects associated with the use of these drugs, such as edema, congestive heart failure, pleural effusion, liver enzyme elevation, myelosuppression, and QT prolongation. Secondary malignancy has been reported as a long-term adverse effect in the patients receiving TKIs. Gunnarsson et al reported that 7.5% (65 out of 868 patients) of Swedish patients diagnosed with CML between 2002 and 2011 developed secondary malignancies with median follow-up of 3.7 (0 to 9.9) years.[12] According to Yin et al, 3.14% (7 out of 223 patients) of Chinese patients developed secondary malignancy after 51 (12–76) months of median duration of treatment of TKIs. Dose of imatinib was 400 and 600 mg for chronic phase and accelerated phase patient, respectively.[13] Duman et al, also reported that patients who had received 400 mg of imatinib developed secondary malignancy and interval between starting TKI therapy and development of malignancy was between 14 months to 7 years.[14] Our patient was exposed to TKIs for 15 years and it is longer than the exposure period reported in the literature. Considering the increasing survival rate of CML patients after TKIs use, it is important to note that secondary malignancy can occur even 10 years or longer after start of TKIs. Roy et al, reported that the incidence of secondary malignancy, especially, prostate cancer increased in a cohort of patients who received IFN-α following treatment with imatinib as therapy for CML.[15] However, it has been revealed that the rates of solid cancers, such as prostate cancer, colorectal cancer, breast cancer, malignant melanoma, pancreas, and kidney cancer, in CML patients were not statistically different from those in general population.[16] But on the other hand, the number of NHL cases was significantly higher in CML patients taking TKIs than in general population.[2]

Several possible mechanisms whereby secondary malignancy may develop in TKI-treated CML patients have been suggested. First, differentiation and function of T lymphocytes is likely affected by TKIs. It has been shown that imatinib disturbs

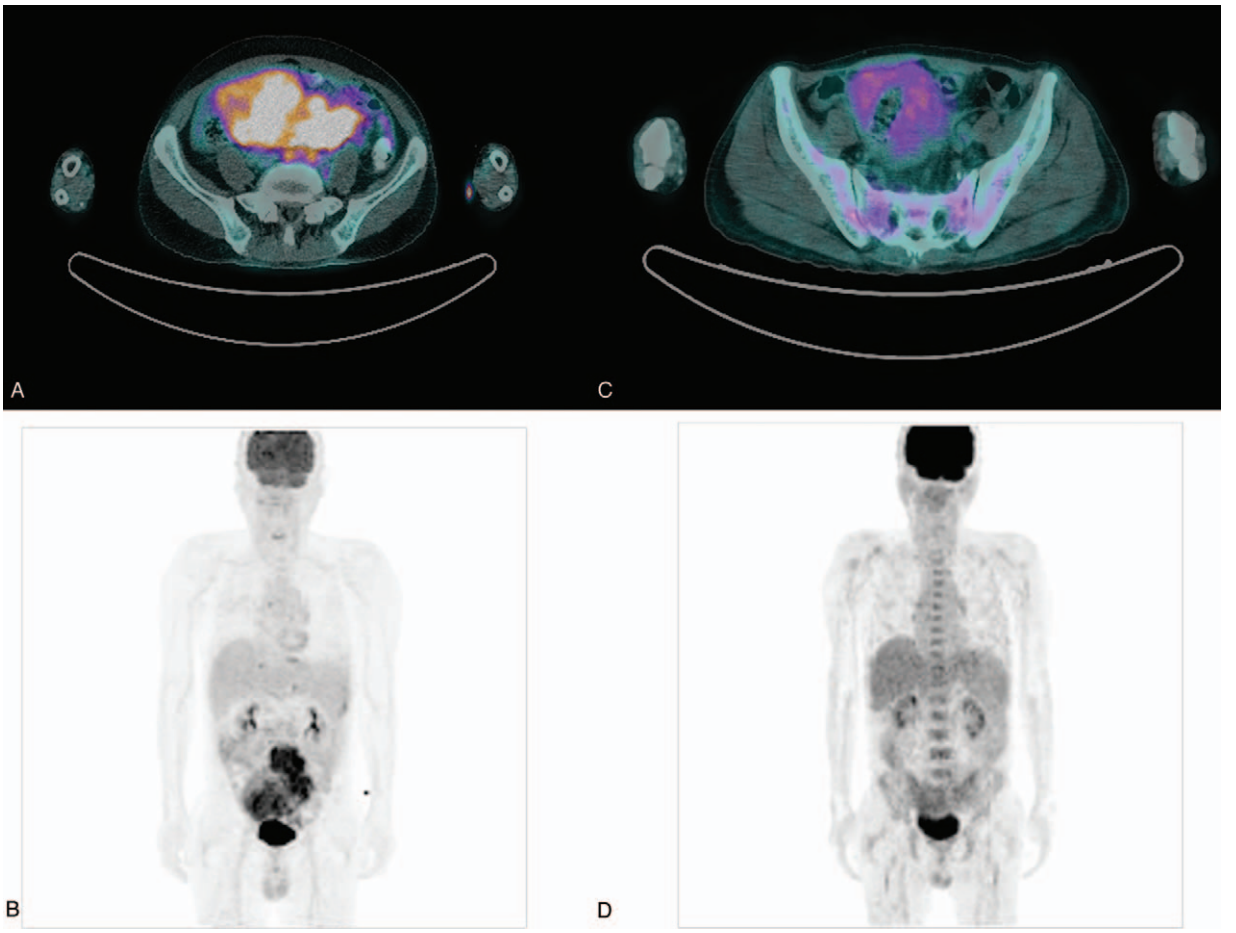

Figure 4. ^{18}F-FDG PET-CT shows that both size and FDG-uptake of the peritoneal mass decreased after 6 cycles of R-CHOP chemotherapy. At the time of diagnosis of LPL (A & B) and after 6 cycles of R-CHOP (C & D).

proliferation of memory cytotoxic T lymphocytes (CTLs) in a murine model, whereas dasatinib exerts even stronger inhibitory effects on human effector T cell functions and proliferation than imatinib.[17,18] Second, differentiation and antigen-presenting function of dendritic cells (DCs) could be disturbed by TKIs. Imatinib inhibits the development of human $CD34^+$ progenitors to DCs, and DCs exposed to imatinib are less potent at inducing primary CTL responses.[19] Rix et al reported that dasatinib also inhibits Bruton's tyrosine kinase, which plays a key role in DC maturation and function.[20]

Not only TKIs targeting BCR/ABL1 but also the inhibitors that block JAK 1/2 for the treatment of myeloproliferative neoplasms have been reported to increase the risk of NHL. Porpaczy et al reported that risk of B-cell lymphomas in MPN patients treated with JAK 1/2 inhibitors (5.8%) was 16-fold higher than that of control group that received conventional treatment (0.36%).[21] Suppression of the JAK/STAT pathway causes dysfunction of CTL and NK cells, and this results in abnormal B-cell clonal expansion. MPN patients developing B-cell lymphoma exhibited mutations in *TP53*, *MYC*, *BCL2*, and *BCL6*.

Our CML patient received imatinib, dasatinib, and radotinib consecutively and was exposed to TKIs for a total of 15 years. We believe that such long-term exposure to TKIs promoted not only dysregulation of immune system but also development of LPL as another malignancy. After the patient was diagnosed with LPL, he was treated with six cycles of R-CHOP chemotherapy. He showed partial response, and we continue monitoring him. *TP53* gene encodes tumor suppressor protein, p53, which activates DNA repair protein and suppresses cell proliferation on DNA damage recognition. It has been reported that TP53 mutation is associated with poor outcome in the majority of B-cell lymphomas, including LPL. Poulain et al reported that WM patients with the mutated *TP53* locus showed shorter median OS (6 years) comparing with that of patients with wild type *TP53* (18 years).[22] *TP53* mutation was detected by NGS in this patient, and he is therefore thought to have a poor prognosis.

4. Conclusion

Despite NHL is one of the most frequent secondary malignancies, LPL has not been reported previously as a secondary malignancy in TKI-treated CML patients. We suggest that sequencing, such as NGS, will help to evaluate the risk of development of secondary malignancy by detection of additional mutations in TKI-treated CML patients. Furthermore, we believe that early diagnosis of secondary malignancies could improve survival of CML patients.

Author contributions

Conceptualization: Jae-Yong Kwak.
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Supervision: Jae-Yong Kwak.
Validation: Ho-Young Yhim.
Writing – original draft: Chang-Hoon Lee.
Writing – review & editing: Ho-Young Yhim.

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