Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7066-21
Intern Med 60: 3149-3153, 2021
http://internmed.jp

【 CASE REPORT 】

BCR/ABL1-positive B-lymphoblastic Lymphoma Successfully Treated with Dasatinib-combined Chemotherapy

Chika Yamada[1], Yoshimitsu Shimomura[1], Kimimori Kamijyo[1], Madoka Kanda-Kato[1], Satoshi Yoshioka[1], Daisuke Yamashita[2] and Takayuki Ishikawa[1]

Abstract:

We herein report a rare case of *BCR-ABL1*-positive B-lymphoblastic lymphoma (B-LBL). An 18-year-old woman had a history of persistent left-sided chest pain. Positron emission tomography showed increased metabolic activity in the fifth rib, duodenum, and pancreas. The pathological findings of the pancreas, duodenum, and bone marrow confirmed the diagnosis of B-LBL. Polymerase chain reaction of duodenum and bone marrow also revealed a minor BCR-ABL1 fusion gene. She was diagnosed with *BCR-ABL1*-positive B-LBL and administered dasatinib and prednisolone. She achieved complete remission two weeks after the initiation of the treatment. She received stem cell transplantation after consolidation chemotherapy and sustained complete remission.

Key words: *BCR-ABL1*, B-lymphoblastic lymphoma, tyrosine kinase inhibitors, dasatinib

(Intern Med 60: 3149-3153, 2021)
(DOI: 10.2169/internalmedicine.7066-21)

Introduction

Lymphoblastic lymphoma (LBL) is a neoplasm of lymphoblasts, committed to either the B- (B-LBL) or T-cell lineage (T-LBL), that accounts for approximately 2% of all lymphomas and is classified in the same category as acute lymphoblastic leukemia (ALL) according to the criteria stipulated by the World Health Organization (1, 2). Among LBLs, B-LBL is a particularly rare disease that accounts for only about 10% of cases (3). Patients with B-LBL present with lower-stage disease than those who present with T-LBL (4). Osteolytic bone lesions and skin lesions are the most common infiltration sites, while mediastinal sites, bone marrow, isolated lymph nodes, visceral sites, or central nervous system involvement are rare (5, 6). The pancreas and duodenum are particularly rare sites of involvement and have only been described in case reports (7, 8).

Several cytogenetic abnormalities or genetic mutations have been reported in patients with B-LBL and B-cell ALL (B-ALL) (2). Although these diseases are classified in the same category, whether or not B-LBL is a distinct entity at the genetic level remains controversial (4). Among cytogenetic abnormalities, *BCR-ABL1* is a fusion gene caused by translocations in 9q34 and 22q11 that activates tyrosine kinase, leading to the proliferation and survival of leukemia cells (9). This fusion gene is the most frequent genetic abnormality in ALL and is associated with a poor prognosis (2). However, *BCR-ABL1* in patients with B-LBL has been documented only in case reports (7, 10-14).

We herein report a case of *BCR-ABL1*-positive B-LBL that presented rare involvement in the rib, duodenum, and pancreas and was successfully treated with dasatinib-combined chemotherapy.

Case Report

An 18-year-old woman first presented to a different hospital with a history of persistent left-sided chest pain for 7 weeks. A complete blood count test showed no specific abnormality, but a biochemical test showed elevated pancreatic amylase levels. Computed tomography showed a mass localized in the pancreatic tail and disproportionate fat stranding around the pancreas. She was diagnosed with pancreatitis

[1]Department of Hematology, Kobe City Medical Center General Hospital, Japan and [2]Department of Pathology, Kobe City Medical Center General Hospital, Japan
Received: January 10, 2021; Accepted: February 16, 2021; Advance Publication by J-STAGE: April 5, 2021
Correspondence to Dr. Yoshimitsu Shimomura, shimomura_0119@yahoo.co.jp

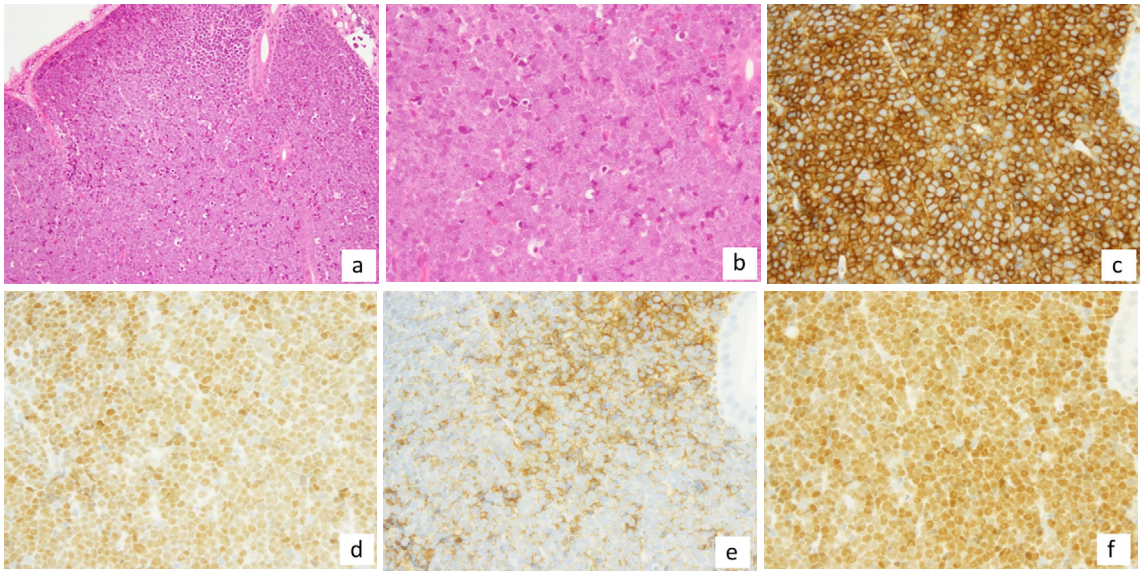

Figure 1. Immunohistochemical features of the pancreas. (a, b) Hematoxylin and Eosin staining shows a massive monotonous lesion comprising medium-sized abnormal cells (a, ×20), (b, ×40). (c–f) Immunohistochemical staining shows that the lymphoblastic cells are positive for PAX5 (c, ×40), TdT (d, ×40), CD34 (e, ×10), and CD10 (f, ×40). PAX5: paired box 5, TdT: terminal deoxynucleotidyl transferase

and administered hydration and antibiotics for treatment. The pancreatitis itself gradually improved. During the examination of the mass of the pancreas, she underwent endoscopic ultrasound-guided fine-needle aspiration. The pathology specimen showed a massive monotonous lesion comprising medium-sized abnormal cells. Immunohistochemical staining revealed that the neoplastic cells were positive for paired box 5 (PAX5), cluster of differentiation 34 (CD34), terminal deoxynucleotidyl transferase (TdT), and CD10 (Fig. 1). She was diagnosed with B-LBL and transferred to our hospital for an intensive examination and treatment.

She had no symptoms at hospitalization, and her superficial lymph nodes, liver, and spleen were not palpable. Complete blood count and biochemical tests showed the following: hemoglobin, 11.7 g/dL; platelet count, 24.1×10^4/μL; white blood cell count, 3.8×10^3/μL with no blast; and lactate dehydrogenase, 188 U/L. A bone marrow sample showed normocellular results, and no evidence of clonal malignant cells was found. A flow cytometric analysis failed to detect clonal malignant cells, but reverse transcription polymerase chain reaction (RT-PCR) revealed a low level of minor *BCR-ABL1* fusion gene transcript (2.1×10^5 copies). Positron emission tomography (PET) showed increased metabolic activities in the fifth rib on the right side, a small part of the pleura close to the rib, duodenum, and pancreas tail (Fig. 2). A biopsy of the white swollen lesions observed in the duodenum was performed using gastroendoscopy (Fig. 2). The pathological findings were similar to those of the pancreatic mass (Fig. 1). A flow cytometric analysis revealed small, abnormal cells that were positive for CD10, CD19, and CD34 and negative for CD20 and CD25. In addition, RT-PCR of the specimen was positive for the minor *BCR-ABL1* fusion gene transcript. Given these findings, she was diagnosed with *BCR-ABL1*-positive B-LBL.

She was administered prednisolone 1 mg/kg/day after the biopsy and dasatinib 140 mg/day after positivity for *BCR-ABL1* was revealed, according to our institutional policy. She achieved complete remission (CR), as documented by PET and gastroendoscopy, two weeks after the administration of dasatinib. Subsequently, she was administered three cycles of alternate hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and MA (methotrexate and cyarabine) plus dasatinib as consolidation. In addition, allogeneic hematopoietic stem cell transplantation was performed from a haplo-matched sibling donor. She maintained complete molecular remission four months after transplantation.

Discussion

We encountered a rare case of *BCR-ABL1*-positive B-LBL. In our case, the patient was first diagnosed with pancreatitis and showed rare involvement sites including the pancreas and duodenum. A pathological examination of the pancreas and duodenum confirmed the diagnosis of B-LBL, and RT-PCR of the duodenum revealed the presence of *BCR-ABL1* transcript. In addition, RT-PCR of bone marrow also showed the presence of *BCR-ABL1* transcript, although the smear, flow cytometric analysis, and fluorescence *in situ* hybridization (FISH) analysis findings were normal. She was diagnosed with *BCR-ABL1*-positive B-LBL and administered reduced-intensity induction therapy consisting of dasatinib and prednisolone, achieving CR soon after initiating the treatment. Our case indicated the importance of

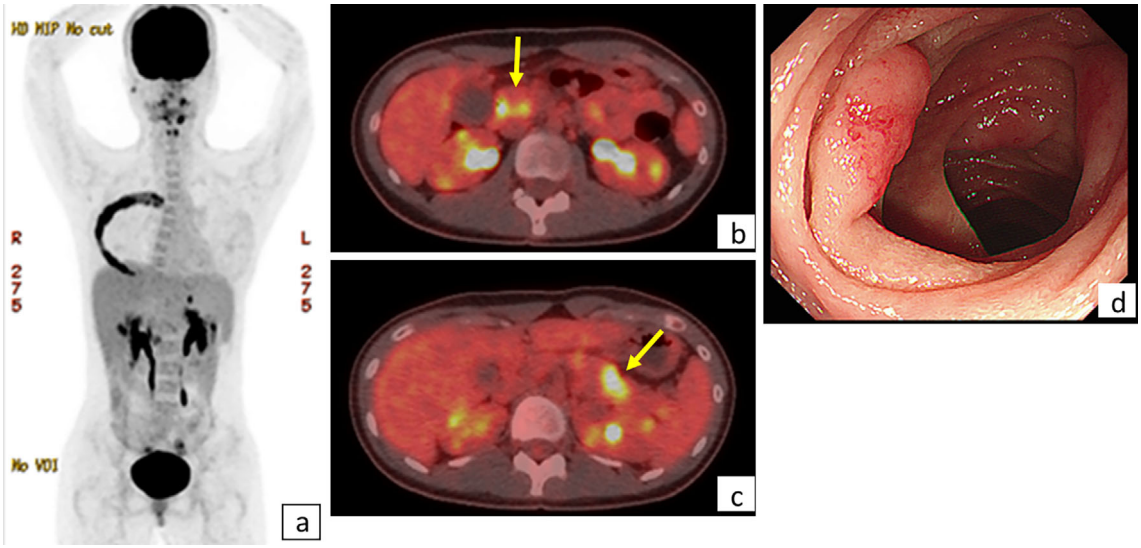

Figure 2. **PET-CT and gastroendoscopy features. PET-CT shows increased metabolic activities in several organs (a); in the whole fifth rib, a small part of the pleura is close to the rib, duodenum (b, arrow), and pancreas tail (c, arrow). Gastroendoscopy of the duodenum shows multiple white, swollen lesions (d, arrow).**

Table. **Summary of Previous Reports.**

Reference	Sex	Age (years)	Involvement sites	First detection of *BCR-ABL1*	Type of BCR/ABL	BM	Treatment	Allo-SCT	Clinical course
10	M	27	First: testis, Relapse: BM, PB	RT-PCR of BM at relapse	n.a.	(At relapse) FCM: 84.3% FISH: n.a. RT-PCR: positive	hyperCVAD/MA Relapse: imatinib, vincristine, prednisolone	-	Suicide
11	M	77	Testis, retroperitoneal lymph node, left pubic symphysis, L5 vertebral body	RT-PCR of BM	minor	FCM: 0.006% FISH: negative RT-PCR: positive	Dasatinib+ R-hyperCVAD	-	Relspse 4 year after the diagnosis.
12	M	31	Paravertebral mass	RT-PCR of BM	minor	FCM: negative FISH: negative RT-PCR: positive	Imatinib→ dasatinib, radiation	+	Sustaining CR for 30 months after SCT.
7	M	26	Distal femur, pancreas, left kidney, multiple lymph nodes	FISH of the biopsies	n.a.	FCM: n.a. FISH: n.a. RT-PCR: n.a.	Dasatinib+ vincristine, dexamethasone	+	Sustaining CR for 4 months after SCT.
14	M	65	Right humerus	FISH of the biopsy	n.a.	FCM: negative FISH: negative RT-PCR: negative	CHOP→ Dasatinib+ hyperCVAD/MA, radiation	-	Sustaining CR for 5 years after diagnosis.
13	F	43	Left parietal skull	FISH of the biopsy	n.a.	FCM: negative FISH: n.a. RT-PCR: n.a.	Dasatinib+ hyperCVAD/MA	+	Sustaining CR for 4 months after SCT.

BM: bone marrow, CHOP: cyclophosphamide, doxorubicin, vincristine and, prednisolone, CR: complete remission, FCM: flow cytometric analysis, FISH: fluorescence in situ hybridization, hyperCVAD: hyperfractionate cyclophosphamide, vincristine, doxorubicin, dexamethasone, MA: methotrexate, high-dose cytarabine, n.a.: not applicable, PB: peripheral blood, R: rituximab, RT-PCR: reverse transcriptional polymerase chain reaction, SCT: stem cell transplantation

screening for *BCR-ABL1* in both biopsied specimens and bone marrow in patients with B-LBL and suggested the effectiveness of tyrosine kinase inhibitors (TKIs) in such cases.

Philadelphia chromosome is identified in approximately 25% of B-ALL cases, which are classified in the same category as B-LBL (2). The frequency of B-LBL with *BCR-ABL 1* is unknown. The incidence of BCR/ABL1-positive B-ALL is rare in children and adolescents and increases progressively with age (15). Conversely, the incidence of LBL is

higher in children and decreases with age (1). Therefore, BCR/ABL1-positive LBL is considered to be rare. Indeed, six reports on B-LBL with *BCR-ABL1* fusion gene transcript have been published, all of which are summarized in Table (7, 10-14). *BCR-ABL1* was detected in biopsied specimens using either a FISH or RT-PCR analysis in all cases. Furthermore, *BCR-ABL1* was detected in the bone marrow using RT-PCR in all cases tested (10-12). In the present case, we identified *BCR-ABL1* in the duodenum and bone marrow using RT-PCR. The detection of *BCR-ABL1* positivity is challenging because *BCR-ABL1* fusion is rare in B-LBL, and FISH or RT-PCR examinations are not routinely performed in many institutions. However, it is essential to check for the presence of *BCR-ABL1* fusion gene transcript in B-LBL because the treatment options differ depending on the presence of this transcript. In addition, an RT-PCR analysis may be useful for achieving a rapid and accurate diagnosis due to its high sensitivity.

B-ALL with *BCR-ABL1* fusion gene has been associated with a poor prognosis, with a 5-year overall survival rate of about 20% (16). TKI plus standard chemotherapy has significantly improved the prognosis in these patients in the past decade. Reduced-intensity induction therapy, consisting of TKIs and steroids, is a major treatment option for *BCR-ABL1*-positive B-ALL patients because it is highly effective and has a low incidence of severe adverse events (17). Regarding the choice of TKI, prospective studies have shown the effectiveness of dasatinib, and it may have some central nervous system penetration. In addition, it is effective against some *BCR-ABL1* mutations that do not respond to i matinib, and it is generally well-tolerated (17-20). Therefore, we have administered dasatinib plus steroids for the initial treatment of *BCR-ABL1*-positive B-ALL.

However, the prognosis and appropriate treatment strategy for *BCR-ABL1*-positive B-LBL remains unclear, mainly because of its rarity. Most reports and guidelines recommend treating patients with B-LBL in accordance with B-ALL (1). In previous reports, the patients who underwent standard chemotherapy without TKI were found to have developed relapse (10). In contrast, all patients who were administered TKI, with or without standard chemotherapy, following the treatment strategy for *BCR-ABL1* positive B-ALL, achieved CR, and many of them sustained CR (7, 11-14). In our case, the patient was first administered reduced-intensity induction therapy consisting of dasatinib and steroid and achieved CR two weeks after the initiation of treatment. This indicates the importance of PCR testing for the immediate detection of *BCR-ABL1* to enable appropriate treatment to be provided to patients with B-LBL.

In conclusion, we encountered a rare case of *BCR-ABL1*-positive B-LBL involving the 5th rib, duodenum, and pancreas. It is important to detect the presence of the *BCR-ABL1* fusion gene transcript, not only in patients with B-ALL but also in those with B-LBL, as the treatment strategy is differs markedly depending on the presence of the gene fusion transcript.

This case report did not require a review by the institutional review board of our hospital. Written informed consent was obtained from the patient.

PCR testing for BCR/ABL and the off-label use of dasatinib for the initial treatment of B-LBL were approved by the Committee for Appropriate Use of Drugs and Medical Devices of Kobe City Medical Center General Hospital.

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

Acknowledgement

The authors thank the medical and nursing staff at Kobe City Medical Center General Hospital.

References

1. Cortelazzo S, Ponzoni M, Ferreri AJM, Hoelzer D. Lymphoblastic lymphoma. Crit Rev Oncol Hematol **79**: 330-343, 2011.
2. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [Internet]. 2017 [cited 2020 Aug 1]. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017
3. Borowitz MJ, Croker BP, Metzgar RS. Lymphoblastic lymphoma with the phenotype of common acute lymphoblastic leukemia. Am J Clin Pathol **79**: 387-391, 1983.
4. Burkhardt B, Hermiston ML. Lymphoblastic lymphoma in children and adolescents: review of current challenges and future opportunities. Br J Haematol **185**: 1158-1170, 2019.
5. Bernard A, Murphy SB, Melvin S, et al. Non-T, non-B lymphomas are rare in childhood and associated with cutaneous tumor. Blood **59**: 549-554, 1982.
6. Lin P, Jones D, Dorfman DM, Medeiros LJ. Precursor B-cell lymphoblastic lymphoma: a predominantly extranodal tumor with low propensity for leukemic involvement. Am J Surg Pathol **24**: 1480-1490, 2000.
7. Alshomar A, El Fakih R. Philadelphia chromosome-positive lymphoblastic lymphoma - Is it rare or underdiagnosed? Hematol Oncol Stem Cell Ther 2018.
8. Iwamuro M, Kawai Y, Yamawaki Y, Takata K, Yamamoto K. Precursor B Lymphoblastic lymphoma Involving the Stomach. Case Rep Gastrointest Med **2013**: e930918, 2013.
9. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. Am J Hematol **95**: 691-709, 2020.
10. Zhu J, Zhang S, Zhu L, et al. Primary testicular Ph-positive B lymphoblastic lymphoma: an unusual presentation and review. Cancer Biol Ther **16**: 1122-1127, 2015.
11. Boddu P, Yin CC, Kanagal-Shamanna R, et al. An unsuspected finding of t(9; 22): a rare case of Philadelphia chromosome-positive B-lymphoblastic lymphoma. Case Rep Hematol **2017**: 2413587, 2017.
12. Dragani M, Andreani G, Fava C, et al. Philadelphia-positive lymphoblastic lymphoma: a case report and review of the literature. Stem Cell Investig **6**: 17, 2019.
13. Sadrzadeh H, Huck AE, Chen Y-B, Hasserjian RP, Fathi AT. Philadelphia chromosome positive B-cell lymphoblastic lymphoma isolated to bone. Leuk Lymphoma **54**: 2052-2054, 2013.
14. Takahashi T, Ichikawa S, Ichinohasama R, Harigae H. BCR-ABL1 positive lymphoblastic lymphoma - Should it be treated like a B-lymphoblastic leukemia with t(9; 22); BCR-ABL1? Leuk Lymphoma **61**: 1265-1267, 2020.
15. Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic

leukemia. J Clin Oncol **35**: 975-983, 2017.

16. Laport GG, Alvarnas JC, Palmer JM, et al. Long-term remission of Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation from matched sibling donors: a 20-year experience with the fractionated total body irradiation-etoposide regimen. Blood **112**: 903-909, 2018.

17. Foà R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood **118**: 6521-6528, 2011.

18. Ravandi F. Current management of Philadelphia chromosome positive ALL and the role of stem cell transplantation. Hematology **2017**: 22-27, 2017.

19. Shen S, Chen X, Cai J, et al. Effect of dasatinib vs imatinib in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: A randomized clinical trial. JAMA Oncol **6**: 358, 2020.

20. Porkka K, Koskenvesa P, Lundán T, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood **112**: 1005-1012, 2008.