Respiratory Medicine Case Reports 37 (2022) 101662

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case Report

Dasatinib-induced massive left chylothorax in a patient with chronic myeloid leukemia

Go Makimoto [a,b,c,*], Mahito Misawa [c], Yoshinobu Maeda [d], Katsuyuki Kiura [a]

[a] Department of Allergy and Respiratory Medicine, Okayama University Hospita, Japanl
[b] Division of Hospital-based Cancer Registry, Okayama University Hospital, 2-5-1 Shikata-cho Kita-ku, Okayama, 700-8558, Japan
[c] Department of Hematology, Ako Central Hospital, 52-6 Somoncho, Ako-City, Hyogo, 678-0241, Japan
[d] Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho Kita-ku, Okayama, 700-8558, Japan

ARTICLE INFO

Keywords:
Chronic myeloid leukemia
Chylothorax
Dasatinib

ABSTRACT

Dasatinib, an effective second-generation tyrosine kinase inhibitor, is used to treat breakpoint cluster region-Ableson-positive chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphocytic leukemia. One common adverse event associated with dasatinib use is fluid retention, including pleural effusion. Chylothorax, however, is a rare adverse event. Although the precise mechanism of dasatinib-induced chylothorax is unclear, almost all cases involve right or bilateral chylothorax, and mostly occur within 5 years of dasatinib initiation. Here, we report a rare case of a patient with dasatinib-induced massive left chylothorax 10 years after dasatinib initiation, which improved after dasatinib termination and a switch to bosutinib.

1. Introduction

Dasatinib, an effective second-generation oral tyrosine kinase inhibitor, is used to treat newly-diagnosed, resistant, or intolerant-to-prior therapy, breakpoint cluster region-Abelson (BCR-ABL)-positive chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphocyte leukemia [1,2]. Dasatinib exhibits activities against ABL, Src, and platelet-derived growth factor receptor (PDGFR) pathways, and induces programmed death of target cells. Common adverse events associated with dasatinib use are skin rash, pancytopenia, nausea, and fluid retention, including pleural effusion [1]. The incidence rate of dasatinib-induced pleural effusion has previously been reported to range from approximately 20%–35% [1,3]. However, dasatinib-induced chylothorax has rarely been reported, and its precise mechanism remains unclear [4]. Furthermore, dasatinib-induced chylothorax has been reported to mostly occur on the right side of the chest, or bilaterally, and within approximately 5 years of dasatinib initiation [4,5]. Therefore, dasatinib-induced left-sided chylothorax occurring much longer after dasatinib initiation is even rarer.

Herein, we present a rare case of a patient with CML and dasatinib-induced massive left-sided chylothorax that occurred 10 years after dasatinib initiation. We reviewed English language publications concerning dasatinib-induced chylothorax in the MEDLINE database.

2. Case report

A 43-year-old man with a 13-year history of CML was treated with imatinib 400 mg daily. Following 2.5 years of imatinib

* Corresponding author. Department of Allergy and Respiratory Medicine, Okayama University Hospital, 2-5-1 Shikata-cho Kita-ku, Okayama, 700-8558, Japan.
E-mail address: gmakimoto5@okayama-u.ac.jp (G. Makimoto).

https://doi.org/10.1016/j.rmcr.2022.101662
Received 5 March 2022; Received in revised form 9 April 2022; Accepted 28 April 2022
Available online 5 May 2022

treatment, a deep molecular response (DMR: $MR^{4.0}$) had not been achieved; therefore, this patient was treated with nilotinib 400 mg twice daily as a second-line therapy. However, a rash developed and the patient was switched to dasatinib 100 mg daily after which a DMR ($MR^{4.5}$) was achieved, lasting >10 years. However, at 123 months post-initiation of dasatinib treatment, the patient complained of dyspnea, but with no fever or chest pain, and was hypoxic. Plain chest radiographic images showed a massive left pleural effusion (Fig. 1). Laboratory data indicated normal renal function with no increase in white blood cell count (5180/μL) or C-reactive protein concentration (0.07 mg/dL) levels.

First, left pleural effusion was suspected due to dasatinib-induced fluid retention, and dasatinib treatment was stopped. However, three weeks later, the left pleural effusion had only decreased slightly. An ultrasound-guided left thoracentesis showed a chylous pleural effusion (Fig. 2) with elevated protein (6.0 g/dL, 86% of serum) and lactate dehydrogenase (160 IU/L, 72% of serum) levels consistent with Light's criteria for exudate effusion [6]. The triglyceride level of the pleural effusion was also very high (1374 mg/dL); therefore, the patient was diagnosed with chylothorax. Having denied any history concerning other possible causes of chylothorax, such as trauma, thoracic surgery, or thoracic malignancies, dasatinib-induced chylothorax was suspected and the patient was subsequently switched to bosutinib treatment. The left pleural effusion then gradually decreased and did not recur.

3. Discussion

We encountered a rare case of left massive dasatinib-induced chylothorax that occurred long after drug initiation. This case was rare for two reasons. First, left massive chylothorax has not been previously reported in the English literature to date. Second, chylothorax occurring >10 years after dasatinib initiation has also not been reported.

CML is a hematopoietic stem cell disorder that induces uncontrolled myeloproliferation. It is often related to Philadelphia chromosome 9 (which contains the ABL kinase domain) and translocation of chromosome 22 (which contains BCR). Dasatinib, a potent second-generation tyrosine kinase inhibitor, inhibits kinases such as BCR-ABL, PDGFR-β, and Src [7]. Therefore, dasatinib has been used as a first-line or second-line treatment for CML.

Chylothorax is generally due to a chyle leak from the thoracic duct into the thoracic space. The major causes of chylothorax are trauma and thoracic surgery. Other causes have been reported, including thoracic malignancy, sarcoidosis, amyloidosis, superior vena cava thrombosis, and lymphangioleiomyomatosis [8]. However, dasatinib-induced chylothorax has rarely been reported, and its precise pathophysiology has not been fully elucidated. One possible mechanism is that dasatinib inhibits PDGFR-β, which regulates angiogenesis and lymphangiogenesis, resulting in the leakage of lymph fluid [9,10]. We reviewed the English literature in the MEDLINE database to investigate the clinical characteristics of dasatinib-induced chylothorax. After excluding articles where only the abstracts had been written in English or with only meeting abstracts available, it was found that nine cases had been reported to date, including this case (Table 1) [4,5,11–16]. Of the nine cases, eight were adults and one was a child. Of the eight adult patients with chylothorax, five (63%) were male and the median age was 67 years (range, 40–73 years). Except for one patient with acute lymphoblastic leukemia, all the patients had been diagnosed with CML. The median duration from dasatinib initiation to chylothorax

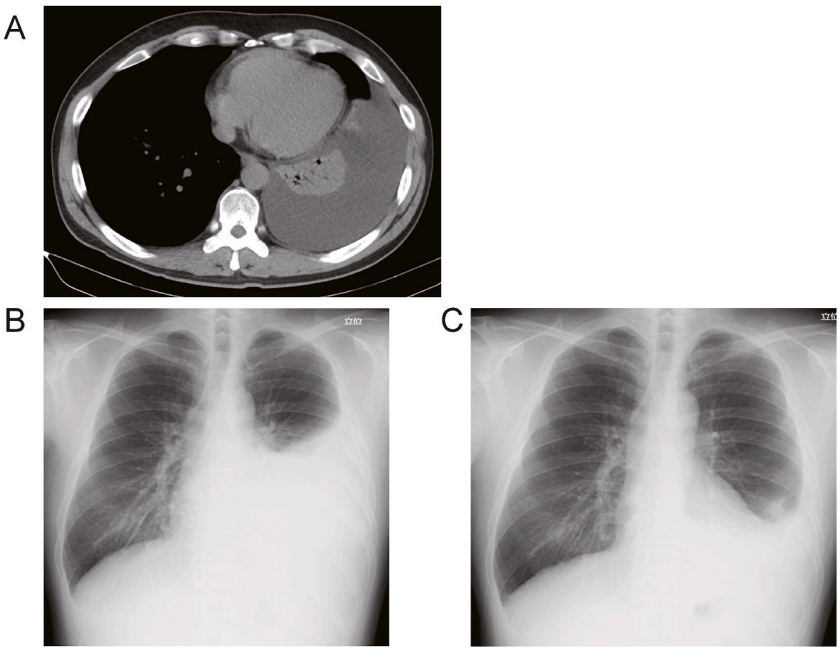

Fig. 1. Improvement of the massive left pleural effusion on plain chest radiographic images
(A) A chest computed tomography image showing the massive left pleural effusion with dasatinib treatment.
(B) A plain chest radiographic image showing the massive left pleural effusion 10 years after dasatinib initiation.
(C) A plain chest radiographic image showing no recurrence of pleural effusion after switching from dasatinib to bosutinib.

Fig. 2. Chylous pleural effusion
Slightly reddish and milky pleural effusion of the left chest was collected using ultrasound-guided thoracentesis.

was 26 months (range, 2–123 months). Hematologic malignancies including lymphoma and chronic lymphocytic leukemia have been reported to be associated with chylothorax [17,18]. However, there have been no reported cases of chronic myelogenous leukemia associated with chylothorax that were not induced by dasatinib. Furthermore, in our case, chylothorax improved after termination of dasatinib and a switch to bosutinib. Therefore, we diagnosed the patient with dasatinib-induced chylothorax.

This case was rare because chylothorax developed >10 years after dasatinib treatment initiation and was left dominant. After excluding other possible causes of chylothorax such as trauma or chest malignancies, the patient was diagnosed with dasatinib-induced chylothorax. Treatment options for dasatinib-induced chylothorax include supportive therapy, such as diuretics or systemic steroids. Switching to other tyrosine kinase inhibitors is an alternative treatment option. In this case, dasatinib was discontinued, the patient was switched to bosutinib, and the chylothorax did not recur thereafter.

4. Conclusion

We encountered a rare case of massive left dasatinib-induced chylothorax occurring long after drug initiation. Most similar cases in previous reports have involved either bilateral or right-sided chylothorax within 5 years of dasatinib initiation; however, this case was left dominant, with the massive chylothorax occurring 10 years after drug initiation. The exact mechanism of dasatinib-induced chylothorax has not been fully elucidated. However, when treating patients with CML with dasatinib, dasatinib-induced chylothorax should be considered as a potential cause of pleural effusion, even if the effusion is left dominant and occurs long after drug initiation.

Statement of ethics

This case report was prepared and completed in accordance with the guidelines of the revised Helsinki Declaration of 2013. Written informed consent was obtained from the patient for publication of the case report and the accompanying images.

Funding sources

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Table 1
Reported cases of dasatinib-induced chylothorax.

Case	Author	Age/ Sex	Disease	Dasatinib		Chylothorax			TKIs Arrangements	Outcome	Ref
				Dose (mg/ day)	Duration (months)	Location	Triglyceride (mg/ dL)	Treatment			
1	Huang et al.	40/F	CML	100	40	BL(R > L)	R:263/L:536	Steroid, diuretic Stop dasatinib	Nilotinib	Improved	(4)
2	Ferreiro et al.	71/F	Ph + ALL	140	2	BL	R:625/L:378	Steroid, diuretic Stop dasatinib	Dasatinib dose reduction	Improved	(5)
3	Baloch et al.	69/M	CML	100	10	R	405	Stop dasatinib	Bosutinib	Improved	(11)
4	Al-Abcha et al.	63/F	CML	100	48	R	700	Stop dasatinib	Nilotinib	Improved	(12)
5	Sasaki et al.	73/F	CML	70	12	R	273	Furosemide plus Japanese herbal medicine "Goreisan"	Imatinib	Improved	(13)
6	Chen et al.	71/M	CML	100	6	BL(R > L)	227	Stop dasatinib	Follow up	Improved	(14)
7	Hickman et al.	5/F	CML	150 mg/m^2/ day	14	BL	603	Stop dasatinib	Follow up	Improved	(15)
8	Hsu et al.	51/M	CML	100	50	BL(R > L)	135	Stop dasatinib	Nilotinib	Improved	(16)
9	**Our Case**	**43/M**	**CML**	**100**	**123**	**L**	**1374**	**Stop dasatinib**	**Bosutinib**	**Improved**	

TKIs, tyrosine kinase inhibitors; Ref., reference; F, female CML, chronic myeloid leukemia; BL, bilateral; R, right; L, left; ALL, acute lymphoblastic leukemia; M, male.

Author contributions

All of the authors contributed to the treatment of the patient.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgment

We would like to thank the patient for providing consent to publish the clinical information and data. We also thank Editage (www.editage.jp) for the English language editing of this manuscript.

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