Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports
OPEN ACCESS
APSR

Dasatinib-induced chylothorax in a patient with chronic myeloid leukaemia: a case report and literature review

Chao-Chin Hsu, Jui-Feng Hsu & Kuan-Li Wu

Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan.

Keywords
Chronic myeloid leukaemia, chylothorax, dasatinib.

Correspondence
Kuan-Li Wu, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, 16ES No.100, Tzyou 1st Rd., Sanmin Dist., Kaohsiung City 80756, Taiwan.
E-mail: 1070476@kmuh.org.tw

Received: 17 February 2021; Revised: 24 March 2021; Accepted: 7 April 2021; Associate Editor: Cameron Sullivan.

***Respirology Case Reports*, 9 (6), 2021, e00753**

doi: 10.1002/rcr2.753

Abstract

Dasatinib is a potent and effective second-generation oral tyrosine kinase inhibitor that is clinically indicated for the treatment of imatinib-resistant or imatinib-intolerant breakpoint cluster region-Abelson (BCR-ABL)-positive chronic myeloid leukaemia (CML) or for Philadelphia chromosome-positive acute lymphocytic leukaemia. The most common adverse events associated with dasatinib therapy are skin rash, gastrointestinal upset, pancytopenia, pulmonary hypertension, and fluid retention, including pleural effusion. However, chylothorax secondary to dasatinib administration has rarely been reported. Although the underlying mechanism leading to dasatinib-induced chylothorax is uncertain, the preferred treatment options are usually supported with diuretics or systemic steroids. Moreover, the discontinuation of the drug is mandatory in refractory cases. Here, we present the case of a patient with dasatinib-induced chylothorax, and review the previously reported cases in the literature.

Introduction

Dasatinib, a potent and effective second-generation oral tyrosine kinase inhibitor, is frequently used for imatinib-resistant or imatinib-intolerant breakpoint cluster region-Abelson (BCR-ABL)-positive chronic myeloid leukaemia (CML) or for Philadelphia chromosome-positive acute lymphocytic leukaemia. Dasatinib, as a multitarget kinase inhibitor, exhibits the activity against ABL, Src, and platelet-derived growth factor receptor (PDGFR) pathways, halting the proliferation and inducing the programmed death of target cells. The most common adverse events associated with dasatinib therapy are skin rash, gastrointestinal upset, pancytopenia, pulmonary hypertension, and fluid retention, including pleural effusion [1–5]. The incidence of dasatinib-associated pleural effusion reported in a previous study was approximately 20% [1]. However, dasatinib-induced chylothorax has rarely been reported and the underlying mechanism is uncertain [2–5]. Here, we present the case of a patient with dasatinib-induced chylothorax.

Case Report

A 51-year-old man with CML, which was diagnosed eight years earlier, was initially treated with imatinib 400 mg daily. Due to CML relapse after three years of treatment, imatinib was replaced with dasatinib 50 mg twice daily. It resulted in major molecular response (MMR) three months later after imatinib was changed to dasatinib. However, the patient subsequently suffered from dyspnoea accompanied by cough and lower limb oedema after 50 months of dasatinib use. Laboratory data revealed normal renal function without increased white blood cell counts (6350/μL) or C-reactive protein (1.02 mg/L). Echocardiography showed adequate systolic function. Chest radiography revealed bilateral pleural effusion. Ultrasound-guided right thoracentesis yielded chylous effusion (Fig. 1) with elevated lactate dehydrogenase (LDH; 133 g/dL, 40% of serum) and protein (3.5 g/dL, 52% of serum) levels. Chylothorax was determined based on the patient's elevated triglyceride level (135 mg/dL). After excluding other possible causes of chylothorax, such as trauma, surgery, or malignancy, dasatinib-induced chylothorax was suspected. Thus, dasatinib was discontinued and replaced by

Figure 1. Chylous pleural effusion. Yellow and milky pleural effusion of the right chest was collected by ultrasound-guided thoracentesis.

nilotinib with the temporary steroid. Afterwards, no recurrence of pleural effusion was recorded in the following imaging check-up (Fig. 2).

Discussion

CML is a disorder of haematopoietic stem cells that results in uncontrolled myeloproliferation. It is mostly related to Philadelphia chromosome, and is created through a translocation of chromosome 9 that contains the ABL kinase domain and a translocation of chromosome 22 that contains a BCR. Dasatinib is a potent and effective second-generation oral tyrosine kinase inhibitor that inhibits kinases including BCR-ABL, PDGFR-β, and Src, among others [6]. Dasatinib has been widely used as a first- or second-line treatment for CML.

Chylothorax is caused by chyle leakage from the thoracic duct into the pleural space, the most common causes of which are trauma and surgery. However, chylothorax can also result from non-traumatic causes including malignancy, sarcoidosis, and superior vena cava thrombosis [7]. It is most likely that the cause of the chylothorax in our case was the dasatinib therapy.

Cases of drug-induced chylothorax are rare, and the pathophysiology of dasatinib-related chylothorax has not yet been fully characterized. One possible mechanism of this complication could be that dasatinib inhibits PDGFR-β, which regulates angiogenesis, lymphangiogenesis, and vascular smooth muscle cell proliferation, resulting in the leakage of lymph fluid into the pleural space [8]. Another possible mechanism is the inhibition of Src kinase by dasatinib. Src is a proto-oncogene encoding a non-receptor tyrosine kinase which is widely expressed in haematopoietic

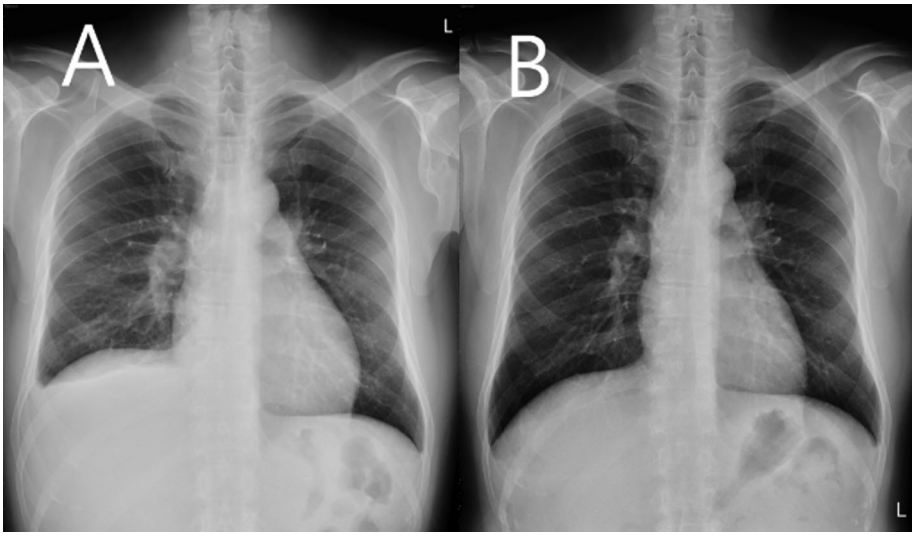

Figure 2. Improvement of pleural effusion on chest plain films. (A) Chest radiograph showed bilateral pleural effusion, especially in the right hemithorax, with the treatment of dasatinib. (B) Chest radiograph showed no recurrence of pleural effusion after the replacement of dasatinib by nilotinib.

Table 1. Reported cases of dasatinib-induced chylothorax.

Case	Age, sex	Subtype of leukaemia	Dasatinib dose (mg/daily)	Duration of dasatinib (months)	Location	Triglyceride (mg/dL)	Treatment for chylothorax	Final treatment
Huang et al. [2]	40, Female	CML	100	40	Bilateral	Right 263/left 536	Thoracentesis, steroid, diuretic, then stop dasatinib	Nilotinib
Ferreiro et al. [3]	71, Female	Ph + ALL	140	2	Bilateral	Right 625/left 378	Thoracentesis, steroid, diuretic, dose reduction	N.A.
Baloch et al. [4]	69, Male	CML	100	10	Right	405	Thoracentesis, dose reduction, then stop dasatinib	Bosutinib
Al-Abcha et al. [5]	63, Female	CML	100	48	Right	700	Thoracentesis, dose reduction, then stop dasatinib	Nilotinib
Sasaki et al. [8]	73, Female	CML	70	12	Right	4300	Furosemide plus Japanese herbal medicine “Goreisan”	Imatinib
Trivedi et al. [10]	62, Male	CML	N.A.	24	Bilateral	603	Prednisone	N.A.
Chua et al. [11]	44, Female	CML	100	36	Right	N.A.	Thoracentesis, then stop dasatinib	N.A.
Korotun et al. [12]	44, Male	CML	N.A.	N.A.	Left	610	Stop dasatinib	Loss of follow-up
Yang et al. [13]	47, Male	CML	100	8	Right	N.A.	Thoracentesis and diuretic	Dasatinib 100 mg daily
Yang et al. [13]	46, Male	CML	100	19	Left	N.A.	Thoracentesis, diuretic, then stop dasatinib	Imatinib
Yang et al. [13]	49, Male	CML	100	30	Bilateral	N.A.	Thoracentesis, diuretic, then stop dasatinib	No treatment
Chen et al. [14]	71, Male	CML	100	6	Bilateral	222	Thoracentesis and stop dasatinib	Following up
Hickman et al. [15]	5, Female	CML	150 mg/m^2 per day	14	Bilateral	603	Thoracentesis and stop dasatinib	Following up
Hsu et al. (our case)	51, Male	CML	100	50	Bilateral	135	Thoracentesis and stop dasatinib	Nilotinib

CML, chronic myeloid leukaemia; Ph + ALL, Philadelphia chromosome-positive acute lymphocytic leukaemia.

cells in lung tissue. It is responsible for capillary integrity, which it maintains by inducing the expression of vascular endothelial growth factor [5].

Animal models given high doses of dasatinib have been found to exhibit altered endothelial barrier integrity due to the production of reactive oxygen species (ROS), which in turn results in increased pulmonary vascular endothelial permeability leading to pleural effusion. It also leads to alterations in the distribution of key proteins for cell–cell junctions, such as VE-cadherin and ZO-1, and to the development of actin stress fibres. The dilatation of lymphatic vessels in lungs with high doses of dasatinib has also been observed in an animal model [9].

To the best of our knowledge, only a small number of cases of dasatinib-induced chylothorax have been reported in previous studies. More specifically, a search of the PubMed database revealed 13 such cases, which are summarized in Table 1 [10–15]. Of those 13 patients, 12 (92%) were adults and one (8%) was a child. Of the adult cases, seven (58%) were male and five (42%) were female. The median age of these dasatinib-induced chylothorax cases was 55 years (with a range from 40 to 71 years). Eleven of those patients (92%) were diagnosed with CML and one of them was diagnosed with acute lymphocytic leukaemia. The median time to chylothorax development was 19 months after dasatinib was introduced. All of the patients had improved symptoms with treatment, such as thoracentesis, steroids, diuretics, or with the discontinuation of the dasatinib. Only one patient continued to receive dasatinib treatment with concurrent diuretics use.

A review of these cases indicated that the management of dasatinib-related pleural effusion can include discontinuation of the drug, thoracentesis, and the administration of diuretics and a short course of prednisone. It also appears to be reversible by the antioxidant agent N-acetylcysteine (NAC) in an animal model [9]. In a Japanese case report, pleural effusion was reported to have been successfully reduced through the administration of the herbal medicine Goreisan [8].

Our patient developed chylothorax after 50 months of dasatinib 100 mg daily to treat CML. Moreover, after the exclusion of other possible causes of chylothorax, the dasatinib treatment was regarded as the most likely cause of the chylothorax. We therefore halted the dasatinib treatment and replaced it with another tyrosine kinase inhibitor, after which the chylothorax did not recur.

In conclusion, this article presents the case of a patient with dasatinib-related chylothorax, as well as a review of similar cases that have been reported in the literature. When a CML patient is treated with dasatinib, chylothorax should be considered as a potential cause of pleural effusion in patients treated with dasatinib. Although the exact mechanism of this complication is still not fully understood, in most reported cases, cessation of dasatinib resolved the chylothorax. Shifting the patient to another tyrosine kinase inhibitor is also an option if the chylothorax is intractable.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Author Contribution Statement

Chao-Chin Hsu conceived the presented idea and wrote the manuscript. Kuan-Li Wu and Jui-Feng Hsu revised the paper critically for important intellectual content. All authors read and approved the final manuscript.

References

1. Brixey AG, and Light RW. 2010. Pleural effusions due to dasatinib. Curr. Opin. Pulm. Med. 16(4):351–356.
2. Huang YM, Wang CH, Huang JS, et al. 2015. Dasatinib-related chylothorax. Turk. J. Haematol. 32(1): 68–72.
3. Ferreiro L, San-Jose E, Suarez-Antelo J, et al. 2016. Dasatinib-induced pleural effusion: chylothorax, an option to consider. Ann. Thorac. Med. 11(4):289–293.
4. Baloch ZQ, Abbas SA, Bhatti H, et al. 2017. Dasatinib-induced chylothorax in chronic myeloid leukemia. Proc. (Bayl. Univ. Med. Cent.). 30(1):71–73.
5. Al-abcha A, Iftikhar MH, Abu Rous F, et al. 2019. Chylothorax: complication attributed to dasatinib use. BMJ Case Reports. 12(12):e231653.
6. Steinberg M. 2007. Dasatinib: a tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. Clin. Ther. 29(11):2289–2308.
7. Doerr CH, Allen MS, Nichols FC 3rd, et al. 2005. Etiology of chylothorax in 203 patients. Mayo Clin. Proc. 80(7): 867–870.
8. Sasaki H, Kimizuka Y, Ogata H, et al. 2019. Successful control of dasatinib-related chylothorax by the Japanese herbal medicine "Goreisan". Intern. Med. 58(21):3139–3141.
9. Phan C, Jutant EM, Tu L, et al. 2018. Dasatinib increases endothelial permeability leading to pleural effusion. Eur. Respir. J. 51(1):1701096.
10. Trivedi PC, Hapangama S, Perez-Batista E, et al. 2017. Dasatinib induced chylothorax. Am. J. Respir. Crit. Care Med. 195:A3479.

11. Chua A, Cleven K, and Appel D. 2016. Chylothorax and PAH after treatment with dasatinib: a case report. Chest 150(4):571A.
12. Korotun M, Agrawal A, and Wang J. 2018. Chylothorax: a rare complication of dasatinib. Chest 154(4):922A.
13. Yang L, Lu N, Jing Y, et al. 2016. Chylothorax related with dasatinib in the treatment of chronic myeloid leukemia: report of 3 cases. Zhongguo Shi Yan Xue Ye Xue Za Zhi 24 (5):1348–1353.
14. Chen B, Wu Z, Wang Q, et al. 2020. Dasatinib-induced chylothorax: report of a case and review of the literature. Invest. New Drugs 38(5):1627–1632.
15. Hickman K, Diaz E, Graham R, et al. 2020. Dasatinib-induced chylothorax in chronic myelogenous leukemia in pediatric patient: report of a case and review of literature. J. Pediatr. Hematol. Oncol. 42(7): e665–e667.