Respiratory Medicine Case Reports 30 (2020) 101052

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

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

A case of imatinib-related obstructive bronchiolitis followed long term

Chika Yajima [a], Nariaki Kokuho [a,*], Kazutoshi Toriyama [a], Junichiro Kawagoe [a], Yuki Togashi [a], Jun Matsubayashi [b], Hideaki Nakayama [a], Yasuhiro Setoguchi [c], Shinji Abe [a]

[a] Department of Respiratory Medicine, Tokyo Medical University, Tokyo, Japan
[b] Department of Pathology, Tokyo Medical University, Tokyo, Japan
[c] Tokyo Medical and Dental University, Tokyo, Japan

ARTICLE INFO

Keywords:
Obstructive bronchiolitis (OB)
Drug-induced lung injury
Imatinib
Nilotinib
Drug-induced OB

ABSTRACT

Obstructive bronchiolitis (OB) is an intractable disease causing stenosis in the surrounding bronchiolar region and bronchiolar lumen obstruction. Causes of OB are lung and hematopoietic stem-cell transplantation, collagen diseases, infections, and foods, but there are very few reports of drug-induced OB [1]. Imatinib is a drug used for the treatment of leukemia, gastrointestinal stromal tumors, etc. Although there are some reports of imatinib-induced lung injury as a complication (Ohnishi et al., 2006; Ma et al., 2003; Yamasawa et al., 2008; Koide et al., 2011) [2–5], OB has not been reported. We have encountered a patient with OB related to imatinib administered for chronic myelogenous leukemia, who we have followed for 10 years. Drug-induced OB is very rare, but our case demonstrates the importance of considering the possibility of airway lesions by evaluating pulmonary function and expiratory computed tomography in patients with respiratory symptoms despite no shading on imaging.

1. Introduction

Obstructive bronchiolitis (OB) is an intractable disease that causes surrounding stenosis in the bronchiolar region and obstruction of the bronchiolar lumen. With advances in transplantation medical care [6], reports of OB have been increasing in recent years as a major cause of death from complications of transplantations. On the other hand, non-transplantation-associated OB, caused by collagen diseases, infections, drugs, foods, etc., have been reported [1], there have been very few reports on drug-induced OB. We encountered a patient who was diagnosed as having imatinib-related OB by pathological analysis, and report this case as we have been able to follow the patient for a long term (10 years).

1.1. Case report

A 54-year-old woman was diagnosed as having chronic myelogenous leukemia (CML) and started imatinib as the first treatment in February X years. After 7 months, she developed a cough and dyspnea. She had no history of pulmonary diseases or dust inhalation, and her smoking history was 18 pack-years. Physical findings were a body temperature of 36.2 °C, an SpO_2 of 98% (room air), and no abnormalities in her respiratory sounds. Blood gas analysis demonstrated a decrease in PaO_2 (72.9 Torr) and $AaDO_2$ expansion. (Table 1). No significant findings were displayed on chest x-ray or inspiration CT, whereas expiration CT displayed a mosaic pattern in the upper lobe and air trapping in the lower lobe (Fig. 1A and B). Respiratory function tests showed a pattern suggestive of peripheral obstructive ventilatory disorder (Table 1).

Histopathological analysis of surgical lung biopsy tissue showed extensive stenosis of the bronchiolar lumen, and fibrous stenosis owing to bronchiolar elastic fiber and collagen fiber proliferation by EVG staining (Fig. 2), and the patient was diagnosed as having OB. The involvement of infection and collagen disease was ruled out by the patient's clinical course and laboratory findings, and there was no history of transplantation or obvious antigen exposure, so we suspected drug-induced lung injury. We predicted imatinib as the causative drug and performed the drug-induced lymphocyte stimulation test (DLST). The DLST was positive, leading to the diagnosis of drug-related OB by imatinib. The patient began treatment with β2 stimulants for her symptoms of dyspnea at the time of onset of symptoms, and imatinib was discontinued 12 days after we suspected OB on pulmonary function tests and expiratory computed tomography (CT). Three-months later, long-acting muscarinic antagonist (LAMA) and inhaled corticosteroids (ICS) were added as symptomatic treatments, because the patient demonstrated a marked decrease in FEV1.0 (−Δ380 mL) and further worsened

* Corresponding author.
E-mail address: s7035@nms.ac.jp (N. Kokuho).

https://doi.org/10.1016/j.rmcr.2020.101052
Received 14 September 2019; Received in revised form 26 March 2020; Accepted 2 April 2020
Available online 4 April 2020

Abbreviations list

AaDO2	partial pressure difference of alveolar-arterial oxygen
CML	chronic myelogenous leukemia
CT	computed tomography scan
DLco	diffusing capacity for carbon monoxide
DLST	drug-induced lymphocyte stimulation test
EVG	elastica van Gieson
FEV1.0	forced expiratory volume in one
FEV1.0%	forced expiratory volume % in one second
FVC	forced vital capacity
ICS	inhaled corticosteroids
LAMA	long-acting muscarinic antagonist
NSIP	nonspecific interstitial pneumonia
OB	obstructive bronchiolitis
OP	organizing pneumonia
PaO2	partial pressure of arterial oxygen
PaCO2	partial pressure of arterial carbon dioxide
PDGFR	platelet-derived growth factor receptor
RV	residual volume
SpO_2	saturation of percutaneous oxygen
TLC	total lung capacity

Table 1
Laboratory and physiological findings.

Hematology			Serological study		
WBC	3,800	/μL	CRP	1.0	mg/dL
Neu	75.6	%	KL-6	261	UmL
Lym	16.1	%	SP-D	42.6	ng/dL
Eos	2.8	%	IgG	1,420	mg/dL
Hb	11.8	g/dL	IgE	34	mg/dL
PLT	2.27×10^4	/μL	ANA	$< \times 40$	
			dsDNA ab	(−)	
Biochemistry			anti-SM ad	(−)	
TP	6.8	g/dL	anti-SSA ad	(−)	
Alb	3.7	g/dL	anti-Jo1 ad	(−)	
AST	21	U/L	anti-CCP ad	(−)	
ALT	18	U/L	MPO-ANCA	(−)	
LDH	233	U/L	PR3-ANCA	(−)	
T-Bil	0.5	mg/dL			
BUN	13.3	mg/dL			
Cr	0.6	mg/dL			
Drug lymphocyte stimulation test			Blood gas analysis (room air)		
imatinib	560	cpm	pH	4.714	
imatinib(S·I)	307	%	PaO_2	72.9	Torr
control	182	cpm	$PaCO_2$	35.2	Torr
			$HCO3^-$	22.2	mEg/L
			AaDo2	33.1	
Pulmonary function tests					
FVC	2.41	L			
%FVC	94.0	%			
FEV1.0	1.2	L			
FEV1.0%	50.2	%			
TLC	3.97	L			
RV	1.57	L			
RV/TLC	39.5	%			
V50/V25	3.14				
DLco/VA	90.1	%			

dyspnea. Regarding the patient's leukemia, she began interferon-α treatment 4 months after discontinuing imatinib treatment, and she went into remission. Her leukemia subsequently recurred 2 years later, and her treatment was changed to nilotinib. However, even after changing to nilotinib, her FEV1.0 and dyspnea did not worsen (Fig. 3).

2. Discussion

OB is an intractable disease causing stenosis in the surrounding bronchiolar region, as well as bronchiolar lumen obstruction. There have been few reports of drug-induced OB, and the causative agents include D-penicillamine, gold, cocaine, talc, tiopronin, busulfan, papaverine (sauropus androgynus juice or powder), psyllium, sulfasalazine, rituximab, and afatinib [6,7]. These drugs are broadly classified into 2 types, i.e., those that are inhaled and those that are orally administered. Inhaled drugs include cocaine, talc, and psyllium. Their effects are caused by physical airway obstruction, and pathological findings are characterized by airway obstruction owing to the filling of the peripheral airways by the drug, as well as associated inflammatory cell infiltration [8,9]. On the other hand, regarding the orally administered drugs, papaverine used as a health food is the most famous, and it is widely known to cause sauropus androgynus-associated OB, owing to the reports of many cases of OB [10]. Regarding the reports of D-penicillamine, gold, tiopronin, and sulfasalazine, as these drugs are regularly used for rheumatoid arthritis and ulcerative colitis, the possibility of OB associated with the underlying disease cannot be completely denied [11]. Furthermore, busulfan has only been reported to increase the risk of transplant-associated OB in hematopoietic stem cell transplantation [12], indicating the difficulty in diagnosing drug-induced OB.

The present patient was taking rebamipide and lansoprazole in addition to imatinib when she first presented to our department. To date, there have been 2 reports of drug-induced lung injury by rebamipide [13,14]. However, all of the patients histologically demonstrated organizing pneumonia (OP) patterns, and no patients with OB patterns have been reported. Lansoprazole-induced lung injury has been reported to show a nonspecific interstitial pneumonia (NSIP) pattern [15]. Although DLST was not performed for these drugs, the patient's symptoms did not worsen upon taking any of these drugs. Therefore, it is unlikely that any of these drugs are the causative drug of OB.

The patient had no indications of obstructive pulmonary disease, such as bronchial asthma or COPD, and CT images displayed no bullae or emphysema. She had no history of transplantation or clear inhalation exposure that could have caused the OB, and we considered no infectious or autoimmune cause, owing to the low levels of inflammatory markers and absence of autoantibodies in the blood tests. DLST is found to be negative in some patients diagnosed with imatinib-induced lung injury [16–18], and hence a definitive diagnosis cannot be made only by DLST. However, if other diseases have been ruled out, we believe that the results of DLST will aid in the diagnosis of drug-related OB with imatinib.

In this patient, shortness of breath appeared 7 months after the start of imatinib administration. Previous reports have demonstrated that the time to onset of imatinib-induced lung injury is between 2 weeks and 10 months [7], whereas the time to onset of drug-induced OB varies widely from 5 weeks to 36 months [7,11,19–28]. Therefore, the onset of OB 7 months after administration of the drug, as observed in this patient, is possible. For the above reasons, we believe that the reliability of our diagnosis is high, because we made our diagnosis after excluding all other possible causes.

Imatinib is normally used for the treatment of leukemia, gastrointestinal stromal tumors, etc. It has been reported that imatinib frequently causes lung injury, resulting in lymphocytic cell inflammation and polypoid intraluminal fibrosis. On the other hand, our present study is the first report to our knowledge demonstrating that imatinib administration can result in OB.

Imatinib is expected to have therapeutic effects against OB after transplantation [29,30], because of its inhibitory actions on fibrocyte migration and differentiation [31,32]. However it is also necessary to pay attention to the paradoxical effect that imatinib per se causes OB. In our present case, the patient was administered nilotinib, a second-generation tyrosine kinase activity inhibitor, for CML recurrence. Nilotinib is also an inhibitor of Bcr-Abl tyrosine kinase activity

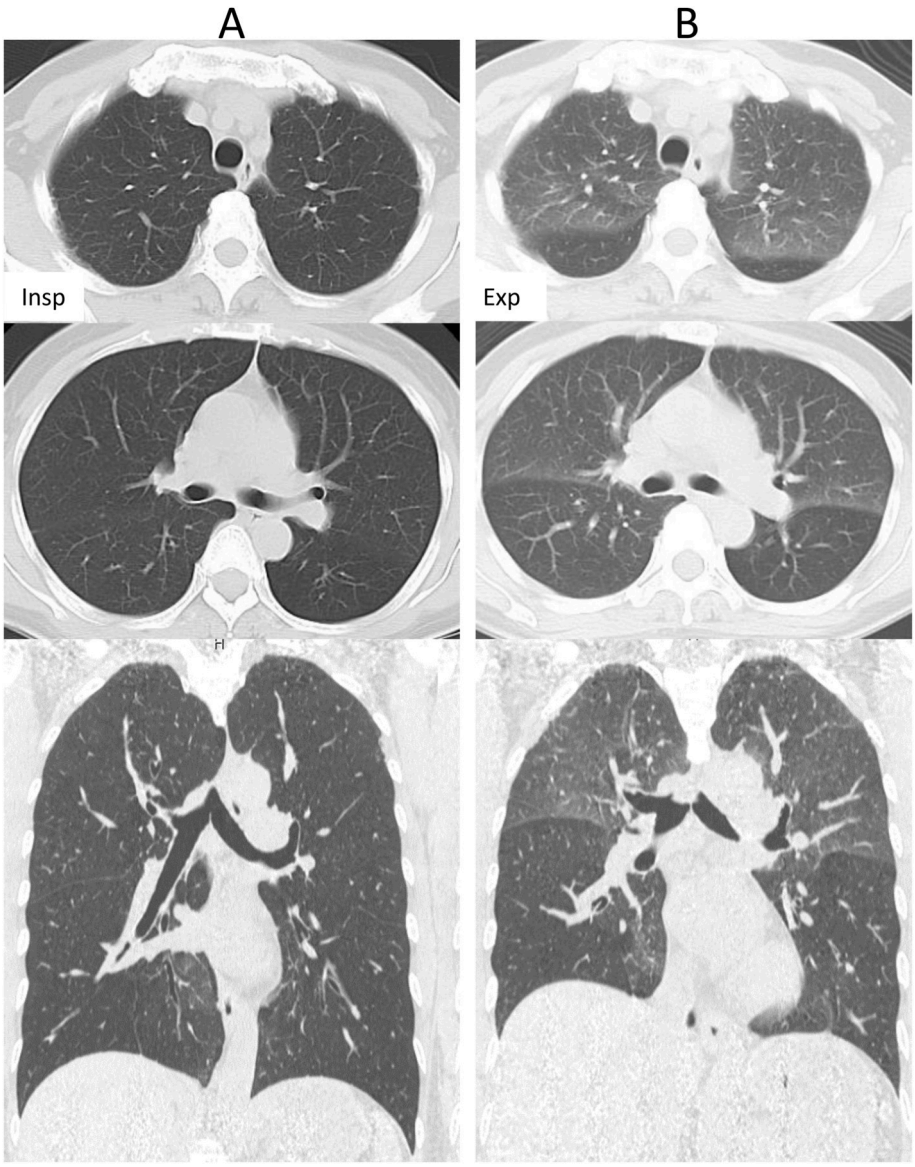

Fig. 1. Chest images of the patient at initial presentation.
No significant findings were seen on chest inspiration CT (A), whereas expiration CT displayed a mosaic pattern in the upper lobe and air trapping in the lower lobe (B).

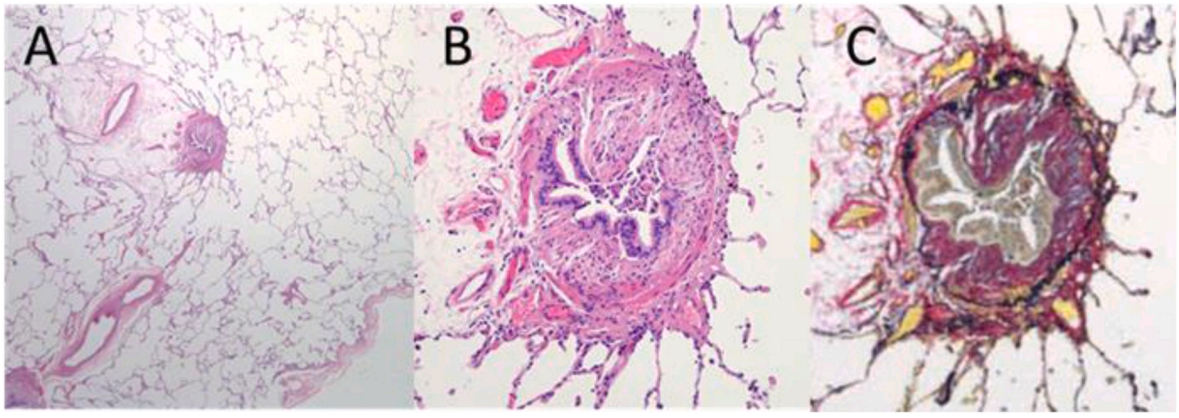

Fig. 2. Histopathological analysis of lung biopsy specimens.
High stenosis was observed in the bronchiolar lumen by Hematoxylin Eosin staining (A, B), and fibrous stenosis owing to bronchiolar elastic fiber and collagen fiber proliferation was observed by EVG staining (C). Magnification:×40, × 400.

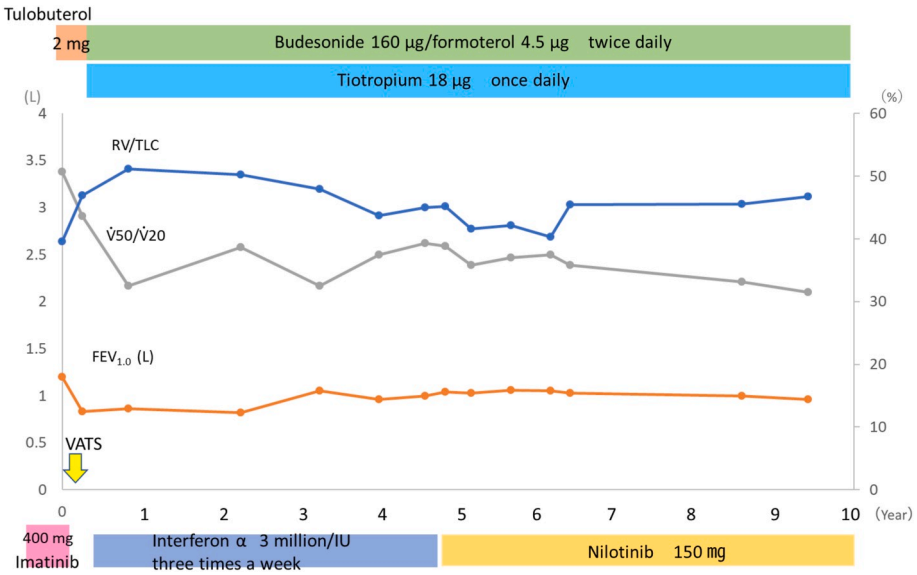

Fig. 3. Treatment course of the patient.
The patient initially started β-stimulant treatment for her dyspnea. Three months after onset, she additionally started LAMA and ICS because her forced expiratory volume in 1 second ($FEV_{1.0}$) decreased markedly and her dyspnea deteriorated. Imatinib was discontinued 12 days after the onset of OB and her treatment was changed to interferon-α, and subsequently to nilotinib at the time of recurrence; however, deterioration of $FEV_{1.0}$ was not observed in the subsequent 10 years.

similar to imatinib. We were concerned about the recurrence of deterioration of OB caused by the use of a drug of the same family, but a decrease in FEV1 was not observed even after administration of nilotinib. Imatinib inhibits the tyrosine kinase activities of Bcr-Abl, v-Abl, c-Abl, platelet-derived growth factor receptor (PDGFR), and KIT, but nilotinib inhibits Bcr-Abl, PDGFR, and KIT. Abl-family kinases are crucial for the proper formation and remodeling of tissues [33,34]. Therefore, we consider the possibility that the active inhibitor component of v-Abl or c-Abl are involved in the onset of OB.

There is presently no effective treatment for OB [20]. Thus, we consider that the absence of FEV1.0 deterioration for 10 years was not owing to the effects of LAMA and ICS, which were administered as symptomatic treatments, but rather that the early discontinuation of imatinib was associated with a better prognosis.

3. Conclusion

We encountered a case of drug-related OB caused by imatinib administration for treatment of CML, in which we were able to follow the patient's course long-term. Drug-induced OB is difficult to detect because unlike normal drug-induced lung injury, it does not cause shadows in the lung field. Therefore, when shortness of breath and cough appear in a patient receiving imatinib, it is important to search for airway lesions, by lung function analysis and expiratory CT. In addition, it is important to suspect the possibility of drug-induced OB and make a definitive diagnosis early, as a more favorable long-term prognosis can be expected by stopping drug administration.

Declaration of competing interest

All authors report no conflicts of interest and have no disclosures or financial support to report.

FVC: forced vital capacity, FEV1.0: forced expiratory volume in one, FEV1.0%: forced expiratory volume % in 1 s, TLC: total lung capacity, RV: residual volume, DLco: diffusing capacity for carbon monoxide, PaO2: partial pressure of arterial oxygen, PaCO2: partial pressure of arterial carbon dioxide, AaDO2: partial pressure difference of alveolar-arterial oxygen.

References

[1] A.F. Barker, A. Bergeron, W.N. Rom, M.I. Hertz, Obliterative bronchiolitis, N. Engl. J. Med. 370 (19) (2014) 1820–1828.
[2] K. Ohnishi, F. Sakai, S. Kudoh, R. Ohno, Twenty-seven Cases of Drug-Induced Interstitial Lung Disease Associated with Imatinib Mesylate, Leukemia, England, 2006, pp. 1162–1164.
[3] C.X. Ma, T.J. Hobday, J.R. Jett, Imatinib Mesylate-Induced Interstitial Pneumonitis, Mayo Clin Proc, England, 2003, pp. 1578–1579.
[4] H. Yamasawa, Y. Sugiyama, M. Bando, S. Ohno, Drug-induced pneumonitis associated with imatinib mesylate in a patient with idiopathic pulmonary fibrosis, Respiration 75 (3) (2008) 350–354.
[5] T. Koide, T. Saraya, K. Nakamoto, A. Nakajima, H. Ishii, M. Fujiwara, H. Shibata, T. Oka, T. Goya, H. Goto, [A case of imatinib mesylate-induced pneumonitis based on the detection of epithelioid granulomas by video-assisted thoracoscopic surgery biopsy in a patient with chronic myeloid leukemia], Nihon Kokyuki Gakkai Zasshi 49 (6) (2011) 465–471.
[6] P.R. Aguilar, A.P. Michelson, W. Isakow, Obliterative Bronchiolitis, Transplantation 100 (2) (2016) 272–283.
[7] N. Kanaji, Y. Chiba, A. Sato, M. Ueno, A. Tadokoro, N. Kita, T. Ishii, N. Watanabe, N. Kadowaki, S. Bandoh, An autopsy case of bronchiolitis obliterans as a previously unrecognized adverse event of afatinib treatment, Respir Investig 55 (1) (2017) 58–62.
[8] L.A. Mc, E. Rogers, K.C. Dunham, Talc pneumoconiosis, Br. J. Ind. Med. 6 (3) (1949) 184–194.
[9] K. Motomatsu, H. Adachi, T. Uno, Two infant deaths after inhaling baby powder, Chest 75 (4) (1979) 448–450.
[10] R.S. Lai, A.A. Chiang, M.T. Wu, J.S. Wang, N.S. Lai, J.Y. Lu, L.P. Ger, V. Roggli, Outbreak of bronchiolitis obliterans associated with consumption of Sauropus androgynus in Taiwan, Lancet 348 (9020) (1996) 83–85.
[11] A. Boehler, P. Vogt, R. Speich, W. Weder, E.W. Russi, Bronchiolitis obliterans in a patient with localized scleroderma treated with D-penicillamine, Eur. Respir. J. 9 (6) (1996) 1317–1319.
[12] L.H. Santo Tomas, F.R. Loberiza Jr., J.P. Klein, P.M. Layde, R.J. Lipchik, J.D. Rizzo, C.N. Bredeson, M.M. Horowitz, Risk factors for bronchiolitis obliterans in allogeneic hematopoietic stem-cell transplantation for leukemia, Chest 128 (1) (2005) 153–161.
[13] H. Kajihara, T. Yoshinaga, S. Usijima, [Case of drug-induced lung injury due to Rebamipide], Nihon Kokyuki Gakkai Zasshi 44 (10) (2006) 716–720.
[14] H. Mochizuki, K. Fujimori, E. Suzuki, M. Arakawa, F. Gejyo, A case of rebamipide-induced pneumonitis, Nihon Kokyuki Gakkai Zasshi 40 (1) (2002) 40–44.
[15] C. Atkins, T. Maheswaran, S. Rushbrook, A. Kamath, Lansoprazole-induced acute lung and liver injury: a case report, Int. J. Clin. Pharm. Ther. 52 (12) (2014) 1102–1104.
[16] E. Iritani, M. Kondo, T. Kanemura, Y. Hara, E. Tagaya, J. Tamaoki, A. Nagai, Drug-induced pneumonia that may have been caused by imatinib mesylate administered for gastrointestinal stromal tumor, Nihon Kokyuki Gakkai Zasshi 45 (7) (2007) 577–581.
[17] A. Uchida, M. Yamamotoa, M. Matsuyamaa, S. Kubota, K. Hatanaka, H. Inouea, Imatinib mesylate-induced organizing pneumonia with disease progression after discontinuation of treatment, diagnosed by surgical lung biopsy, Nihon Kokyuki Gakkai Zasshi 5 (4) (2016) 208–212.
[18] T. Yokoyama, K. Miyazawa, E. Kurakawa, A. Nagate, T. Shimamoto, K. Iwaya, S. Akata, M. Aoshima, H. Serizawa, K. Ohyashiki, Interstitial Pneumonia Induced by Imatinib Mesylate: Pathologic Study Demonstrates Alveolar Destruction and Fibrosis with Eosinophilic Infiltration, Leukemia, England, 2004, pp. 645–646.
[19] K.C. Murphy, C.J. Atkins, R.C. Offer, J.C. Hogg, H.B. Stein, Obliterative bronchiolitis in two rheumatoid arthritis patients treated with penicillamine, Arthritis Rheum. 24 (3) (1981) 557–560.

[20] T. Williams, L. Eidus, P. Thomas, Fibrosing alveolitis, bronchiolitis obliterans, and sulfasalazine therapy, Chest 81 (6) (1982) 766–768.
[21] L. Holness, J. Tenenbaum, N.B. Cooter, R.F. Grossman, Fatal bronchiolitis obliterans associated with chrysotherapy, Ann. Rheum. Dis. 42 (5) (1983) 593–596.
[22] M.A. van de Laar, C.J. Westermann, S.S. Wagenaar, H.J. Dinant, Beneficial effect of intravenous cyclophosphamide and oral prednisone on D-penicillamine-associated bronchiolitis obliterans, Arthritis Rheum. 28 (1) (1985) 93–97.
[23] J.G. Fort, H. Scovern, J.L. Abruzzo, Intravenous cyclophosphamide and methylprednisolone for the treatment of bronchiolitis obliterans and interstitial fibrosis associated with crysotherapy, J. Rheumatol. 15 (5) (1988) 850–854.
[24] A. Demaziere, Y. Maugars, S. Chollet, A. Prost, Non-fatal bronchiolitis obliterans possibly associated with tiopronin. A case report with long-term follow-up, Br. J. Rheumatol. 32 (2) (1993) 172–174.
[25] K.J. Schwartzman, D.M. Bowie, C. Yeadon, R. Fraser, E.D. Sutton, R.D. Levy, Constrictive bronchiolitis obliterans following gold therapy for psoriatic arthritis, Eur. Respir. J. 8 (12) (1995) 2191–2193.
[26] S. Takayama, T. Ogawa, S. Tominaga, M. Yasui, S. Ohno, M. Ohkochi, N. Inase, H. Miura, [Penicillamine-induced bronchiolitis obliterans diagnosed by transbronchial lung biopsy], Nihon Kokyuki Gakkai Zasshi 44 (2) (2006) 128–133.
[27] T. Shen, S. Braude, Obliterative bronchiolitis after rituximab administration: a new manifestation of rituximab-associated pulmonary toxicity, Intern. Med. J. 42 (5) (2012) 597–599.
[28] S. Katsenos, E.M. Antonogiannaki, K. Psathakis, Sulfasalazine-induced hypereosinophilic obliterative bronchiolitis, Arch. Bronconeumol. 52 (2) (2016) 108.
[29] S. Watanabe, Y. Waseda, H. Kimura, H. Takato, K. Ohata, Y. Kondo, K. Kasahara, S. Nakao, Imatinib for Bronchiolitis Obliterans after Allogeneic Hematopoietic Stem Cell Transplantation, Bone Marrow Transplant, England, 2015, pp. 1250–1252.
[30] M. Stadler, R. Ahlborn, H. Kamal, H. Diedrich, S. Buchholz, M. Eder, A. Ganser, Limited Efficacy of Imatinib in Severe Pulmonary Chronic Graft-Versus-Host Disease, Blood, United States, 2009, pp. 3718–3719, reply 3719-20.
[31] J.H. Distler, A. Jungel, L.C. Huber, U. Schulze-Horsel, J. Zwerina, R.E. Gay, B. A. Michel, T. Hauser, G. Schett, S. Gay, O. Distler, Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis, Arthritis Rheum. 56 (1) (2007) 311–322.
[32] S. Watanabe, K. Kasahara, Y. Waseda, H. Takato, S. Nishikawa, T. Yoneda, J. Hara, T. Sone, M. Abo, H. Kimura, S. Nakao, Imatinib ameliorates bronchiolitis obliterans via inhibition of fibrocyte migration and differentiation, J. Heart Lung Transplant. 36 (2) (2017) 138–147.
[33] W.D. Bradley, A.J. Koleske, Regulation of cell migration and morphogenesis by Abl-family kinases: emerging mechanisms and physiological contexts, J. Cell Sci. 122 (Pt 19) (2009) 3441–3454.
[34] P.J. Woodring, T. Hunter, J.Y. Wang, Regulation of F-actin-dependent processes by the Abl family of tyrosine kinases, J. Cell Sci. 116 (Pt 13) (2003) 2613–2626.