

A Suspected Case of an Alveolar Haemorrhage Caused by Dasatinib

Yoritake Sakoda, Yojiro Arimori, Masakatsu Ueno and Takafumi Matsumoto

Abstract

A 39-year-old man treated with dasatinib for chronic myelogenous leukaemia presented to our hospital with haemoptysis, coughing, and dyspnoea. Chest radiography and computed tomography revealed ground-glass opacities and a crazy-paving pattern. Bronchoalveolar lavage was not performed due to serious hypoxemia and bleeding. Significant bleeding from the peripheral bronchi led to a diagnosis of an alveolar haemorrhage. Dasatinib-induced alveolar haemorrhaging was suspected based on the clinical findings. His condition improved immediately after dasatinib withdrawal and initiation of steroid therapy. Reports of alveolar haemorrhaging induced by dasatinib are rare. As such, this is considered an important case.

Key words: alveolar haemorrhage, dasatinib, chronic myelogenous leukaemia

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Introduction

Imatinib is a BCR-ABL tyrosine kinase inhibitor first introduced in 2001 that has markedly improved the prognosis of patients with chronic myelogenous leukaemia (CML). Nilotinib and dasatinib are second-generation tyrosine kinase inhibitors first introduced in 2009 that led to better outcomes than imatinib for the treatment of CML. However, these drugs also have various adverse effects. Here, we report a rare case of alveolar haemorrhaging induced by dasatinib.

Case Report

The patient was a 39-year-old man (height, 176 cm; weight, 107.9 kg; body mass index, 34.8) with a history of hypertension and CML. CML was diagnosed one year prior to the presentation and treated with dasatinib, with a good response. The patient was also on rabeprazole, amlodipine, and azilsartan. He had not been receiving other medications, including health foods or supplements. His coughing began two weeks before presentation. Haemoptysis appeared suddenly, followed by dyspnoea, and he was taken to the hospital in an ambulance. His vital signs were as follows: blood

pressure 172/92 mmHg, pulse 115 beats/min, temperature 38.3°C, percutaneous oxygen saturation 85% (reservoir mask 10 L/min), and respiration 31 breaths/min. Coarse crackling was audible in both lungs. The peripheral leukocyte count was 6,360/ μ L, and the serum C-reactive protein level was 0.9 mg/dL (Table). Blood tests did not reveal any coagulation abnormality. His levels of brain natriuretic peptide (BNP) were mildly elevated (32.8 ng/mL), and the levels of sialylated carbohydrate antigen (KL-6) and surfactant protein-D (SP-D) were also elevated (836 U/mL and 259.6 ng/mL, respectively). The tests for autoantibodies were negative, including the findings for anti-neutrophil cytoplasmic antibody (ANCA). A sputum culture was negative for bacteria, including acid-fast bacilli. Chest X-ray revealed ground-glass opacity and consolidation in both lungs (Fig. 1). Chest computed tomography revealed diffuse ground-glass opacity and consolidation in both lungs around the bronchial vascular bundles, along with a crazy-paving pattern (Fig. 2). The differential diagnosis included respiratory infection, interstitial pneumonia, alveolar haemorrhaging, and heart failure. There was no oedema in the lower extremities, and his cardiac function was within the normal range based on the findings of echocardiography. Thus, the mild brain-type natriuretic peptide (BNP) elevation was considered to be due to his high blood pressure, and heart fail-

Table. Laboratory Date on Admission.

Hematology		Immunology	
Red blood cell count	418×10 ⁴ /μL	Anti-nuclear antibody	(-)
Hemoglobin	12 g/dL	Rheumatoid factor	<5 IU/mL
Hematocrit	35.9 %	MPO-ANCA	<1.0 U/mL
White blood cell count	6,360 /μL	PR3-ANCA	<1.0 U/mL
Neutrophil	63 %	Anti-GBM antibody	<2.0 U/mL
Eosinophil	1 %		
Basocyt	0 %	Biochemistry	
Lymphocyte	33 %	Total Protein	7.3 g/dL
Monocyte	3 %	Albumin	4.5 g/dL
Platelet count	16.9×10 ⁴ /μL	Total bilirubin	0.49 mg/dL
		AST	20 IU/L
		ALT	20 IU/L
		LDH	247 IU/L
		ALP	127 IU/L
		γGTP	43 IU/L
		Urea nitrogen	14.4 mg/dL
		Creatinine	0.79 mg/dL
		Glucose	113 mg/dL
		Sodium	144 mEq/L
		Potassium	3.88 mEq/L
		Chloride	105.7 mEq/L
		Blood gas analysis(O ₂ 10l/min reservoir mask)	
		ph	7.382
		PaO ₂	61 Torr
		PaCO ₂	44.3 Torr
		HCO ₃ ⁻	25.7 mEq/L
		BE	0.9 mEq/L
		SaO ₂	85 %

PT:prothrombin time, PT-INR:prothrombin time international normalized ratio, APTT:activated partial thromboplastin time, FDP:fibrinogen degradation products, CRP:C-reactive protein, KL-6:sialylated carbohydrate antigen, SP-D:surfactant protein-D, CMV:cytomegalovirus, MPO-ANCA:myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA:proteinase3 anti-neutrophil cytoplasmic antibody, GBM:glomerular basement membrane, AST:aspartate aminotransferase, ALT:alanine aminotransferase, LDH:lactate dehydrogenase, ALP:alkaline phosphatase, γGTP:gamma glutamyl transpeptidase, BE:base excess

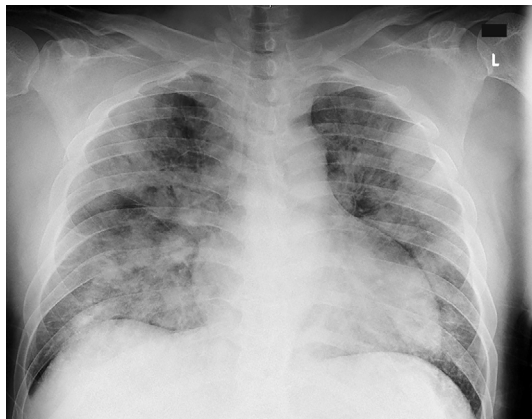


Figure 1. Chest roentgenogram on admission shows bilateral ground-glass opacity and consolidation.

ure was ruled out. Bronchoalveolar lavage (BAL) was not possible due to severe hypoxemia. His symptoms and imaging findings suggested the possibility of alveolar haemorrhaging, and treatment was initiated accordingly.

Given the possibility of drug-induced alveolar haemorrhaging, all oral medications (rabeprazole, amlodipine, azilsartan, and dasatinib) were withdrawn after hospitalisation. We started steroid pulse therapy with methylprednisolone at

1 g/day for 3 days just after hospitalisation. Although there was little increase in the inflammation and no elevation of procalcitonin, we initiated meropenem, micafungin, and ganciclovir given the possibility of infection complicated by his immunocompromised state owing to haematological malignancy and chemotherapy. Respiratory failure progressed on the second day after hospitalisation, so tracheal intubation was performed and respiratory management initiated. We performed a bronchoscopic examination just after intubation, which revealed significant intratracheal haemoptysis and bleeding in the peripheral bronchi. BAL was not possible due to the patient's severe hypoxemia and active bleeding, but alveolar haemorrhaging was strongly suspected based on intratracheal bleeding. His respiratory status and imaging findings improved immediately with steroid pulse therapy (Fig. 3). Maintenance therapy was initiated with methylprednisolone at 80 mg/day after the completion of steroid pulse therapy. Artificial respiration was terminated on Day 8 after hospitalization, and oxygen therapy was ended on Day 9. The steroid administration was tapered, and no signs of recurrence were observed. The patient was considered fit to be discharged on Day 33.

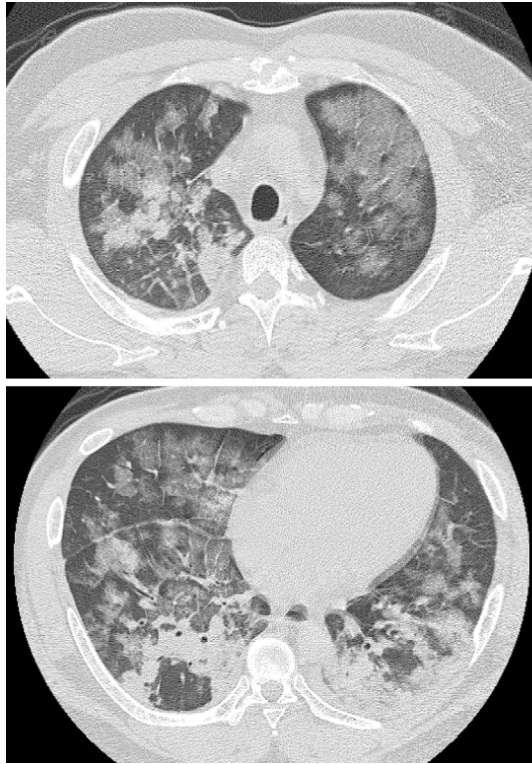


Figure 2. Chest CT on admission shows ground-glass opacity and consolidation in both lungs around bronchial vascular bundles, along with crazy-paving pattern.

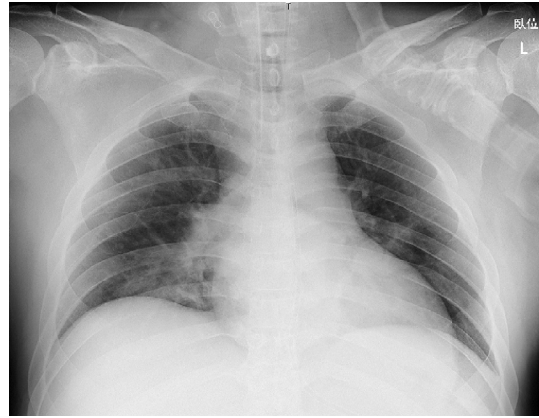


Figure 3. Chest roentgenogram 4 days after administration of PSL therapy revealed remarkable improvement.

Discussion

Dasatinib is a molecular-targeting drug that inhibits BCR-ABL tyrosine kinase, which is involved in the aetiology of CML and Philadelphia-chromosome-positive acute lymphoid leukaemia. The activity of dasatinib is 325 times that of imatinib, and it has become an important drug for CML treatment (1). However, there are reports of adverse effects such as bone marrow suppression, bleeding (cerebral haemorrhaging, lower endocranial bleeding and gastrointestinal bleeding), and body fluid retention (2, 3). In the respiratory system, pleural effusion and interstitial pneumonia are serious adverse effects (4).

Only a few cases of alveolar haemorrhaging have been reported in post-marketing surveillance. Our literature search retrieved only one case report that was presented at a meeting in Japan (5). BAL fluid is considered important for the definitive diagnosis of alveolar haemorrhaging (6). Unfortunately, we were unable to perform BAL due to serious hypoxemia, but we did observe significant intratracheal haemoptysis just after tracheal intubation. The presence of bleeding from the trachea suggested bleeding in the peripheral respiratory tract and alveoli, and computed tomography also revealed subpleural sparing opacities and a crazy-paving pattern, with superimposition of ground-glass opacities and the reticular pattern, which did not rule out the possibility of alveolar haemorrhage (7-9). These observations led to a clinical diagnosis of alveolar haemorrhaging.

Diseases resulting in alveolar haemorrhaging include ANCA-related vasculitis, collagen diseases (e.g. systemic lupus erythematosus), Goodpasture syndrome, heart failure, and adverse drug effects (10). Antinuclear antibodies, myeloperoxidase-ANCA, proteinase 3-ANCA, and anti-glomerular basement membrane antibodies were all negative in our case. We also did not detect any signs of heart failure on a physical examination or in the laboratory findings, including echocardiography. This led us to consider the possibility of drug-induced alveolar haemorrhaging. Our patient was taking rabeprazole, amlodipine, and azilsartan, as well as dasatinib. It was not clear which drug caused the alveolar haemorrhaging, so all of the drugs were discontinued after hospitalisation. After discontinuation of artificial respiration, all of the drugs except dasatinib were reinitiated, and there was no recurrence of alveolar haemorrhaging. Thus, we concluded that dasatinib was the cause of the alveolar haemorrhage.

Drugs often reported to induce pulmonary haemorrhaging include anticoagulants (11), propylthiouracil (12), amiodarone (13), and methotrexate (14). The mechanism underlying haemorrhage can be divided into three categories: 1) excessive anticoagulant therapy, 2) type 3 or 4 allergy, and 3) cytotoxicity (15). The suggested cause of pulmonary complications induced by dasatinib, such as pleural effusion and interstitial pneumonia, is the inhibition of platelet-derived growth factor (16) and participation of large granular lymphocytes (17, 18); however, the exact mechanism is unknown. KL-6 and SP-D levels were elevated in our case, possibly suggesting at least the involvement of alveolar epithelial and interstitial damage. In our case, alveolar haemorrhaging developed approximately one year after initiating dasatinib. The onset of drug-induced lung injury varies from a few days to several years with drug treatment and can last for several months after drug cessation (12, 14). It is therefore difficult to estimate the exact time of onset (19). Since each drug has a characteristic onset pattern, the accumulation of cases is important.

Our case will require continuous medical treatment for CML and the patient is now receiving nilotinib. Nilotinib is

a BCR-ABL tyrosine kinase inhibitor like dasatinib but is reported to have few cross-intolerances (20) and is considered safe (21). However, there are reports of cross-intolerance among BCR-ABL tyrosine kinase inhibitors such as dasatinib. Dasatinib use will continue to increase in the future for the treatment of CML. Alveolar haemorrhaging is a potentially fatal adverse effect, similar to pleural effusion and interstitial pneumonia, and thus should be a consideration when using the drug.

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

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