Obstructive bronchiolitis (OB) is an intractable disease that causes stenosis in the surrounding bronchiolar region and obstruction of the bronchiolar lumen. 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 expired 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 SpO2 of 98% (room air), and no abnormalities in her respiratory sounds. Blood gas analysis demonstrated a decrease in PaO2 (72.9 Torr) and AaDO2 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 stenosing OB 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
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 β-penicillamine, gold, cocaine, talc, tiopronin, busulfan, papaverine (saurophytum androgynus juice or powder), psyllium, sulfasalazine, rituximab, and astatin [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 saurophytum androgynus-associated OB, owing to the reports of many cases of OB [10]. Regarding the reports of β-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 lanosprazole 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.
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 FEV1.0 was not observed even after administration of nilotinib. Nilotinib inhibits the tyrosine kinase activities of Bcr-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 [28]. 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.

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