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Recurrent spontaneous pneumothorax under nintedanib treatment in interstitial lung disease associated with systemic sclerosis

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Abstract. Interstitial lung disease (ILD) is a common complication that can develop during the course of systemic sclerosis (SSc). Nindetanib is an antifibrotic drug approved for the treatment of systemic sclerosis-associated interstitial lung disease. Although there is an insufficient data on the development of pneumothorax, the safety of Nintedanib treatment is also uncertain. We observed recurrent resistant pneumothorax under nintedanib treatment in a patient with systemic sclerosis-associated interstitial lung disease. Nintedanib use may increase the risk of developing refractory pneumothorax. Ssc patients who are started on nintedanib should be followed carefully for pneumothorax.

Key words: systemic sclerosis, spontaneus pnomotorax, nintedanib

Introduction

A 43-year-old male patient was being followed up with ILD associated with systemic sclerosis. He was diagnosed in 2013 and since then he has taken various immunosuppressive treatments such as azathioprine, hyroxychloroquine, prednisolone and cyclophosphamide. In HRCT, fibrosis was observed in 20-30% of the parenchyma area (Figure 1-E). In the patient with FVC 3680 mL (80% predict) in pulmonary function tests and 340 mL annual FVC decrease in DLCO 70% follow-up in one year, it was predicted that the FVC decrease would increase further, and nintedanib 150 mg twice a week was started. At the time the patient was started on nintedanib, Bosentan, diltiazem HCL, sildenafil, methylprednisolone, hydroxychloroquine, acetylsalicylic acid, pantoprazole, calcium carbonate cholecalciferol.

Since the patient did not have gastrointestinal symptoms, the dose was not titrated. Nine months after the start of nintedanib, the patient presented to the emergency department because of dyspnea. Pneumothorax was observed in the right hemithorax in the thorax CT of the patient with Spo2 70 (Figure 1 A-B). The patient was hospitalized and a chest tube was inserted. The patient, whose lung expansion was provided, was hospitalized again with the diagnosis of pneumothorax 1 month after discharge. Drainage was done with a chest tube. Nintedanib was continued after the first pneumothorax. Upon re-development of pneumothorax during hospitalization, pleurodesis and wedge resection were performed with right vats (Figure 1 C-D). Nintedanib was stopped after surgery. The air leak disappeared.

Discussion

We started nintedanib treatment for the patient who developed pulmonary dysfunction and fibrosis,

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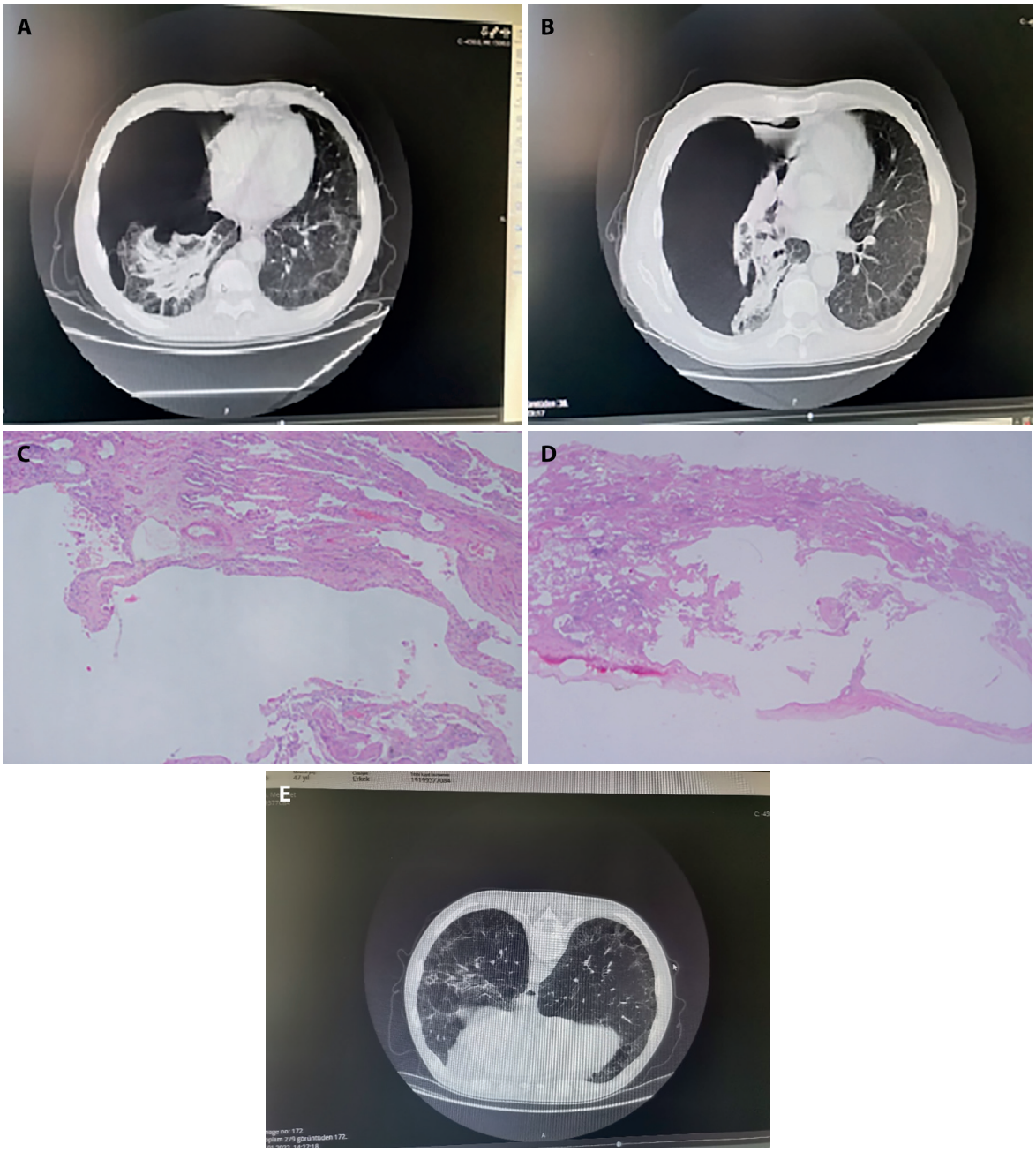

Figure 1. A) Severe pneumothorax was observed in the right hemithorax. Consolidations including air bronchograms with peribronchial reductions in the right lung parenchyma were noted. B) An appearance consistent with a pneumothorax reaching a depth of 7.5 cm in the right hemithorax was observed. C) There is a large bullous focus in the lung, followed by emphysematous areas and chronic inflammation findings in the interstitium (Hematoxylin and eosin, x10). D) It is noteworthy that the bulla wall is lined by alveolar epithelial cells and interstitial areas show chronic inflammatory cell infiltration and fibrosis (Hematoxylin and eosin, x40). E) HRCT before nintedanib. Linear and reticular density increases accompanied by subpleural and peripheral micro and macrocystic honeycomb lung areas are observed in both lungs.

who was followed up for SSc-related ILD. In the course of treatment, we encountered recurrent pleurodesis despite chest tube drainage and spontaneous pneumothorax requiring surgery. It should be kept in mind that pneumothorax may occur during nintedanib therapy for reduced lung function in cases of SSc-ILD.

ILD is a complication with severe irreversible pulmonary dysfunction, and the use of

immunosuppressive drugs may increase the risk of infection and death (1).

In elderly patients, ILD progression is considered a common disease with severely impaired lung function and poor prognosis (2).The SENSCIS study showed that Nintedanib reduced the annual FVC decline and relatively improved lung function in SSc-ILD patients (3).

Nindetanib has no immunosuppressive effect due to its mechanism of action. There is currently no evidence of any benefit in the treatment of patients with severe pulmonary dysfunction. Therefore, evaluating the risks and benefits when administering nintedanib to patients with high lung dysfunction is necessary.

it was also not reported in more than 5% of cases in the INPULSIS trial among patients with idiopathic pulmonary fibrosis (IPF) (3).

However, these clinical studies included patients with relatively good lung function with an estimated mean FVC above 70%. the patient described here met the exclusion criteria of the SENSCIS study (ILD ≥ 10%, %FVC ≥40%, and 30% ≤%DLCO ≤89%). Patients with similar characteristics were not included in the SENSCIS study, and the safety profile of nintedanib is currently largely unknown in this population. Spontaneous pneumothorax in IPF cases is a frequent and increasing complication as the disease progresses (5).

Nintedanib is a small-molecule tyrosine kinase inhibitor against vascular endothelial growth factor (VEGF) receptor (VEGFR), platelet- derived growth factor receptor-alpha (PDGFRα), and fibroblast growth factor receptor (FGFR). Bevacizumab is an agent that causes ischemic changes and perforation in lung tissue due to its anti-VEGF effect (5).

Similar to the effect of bevacizumab in nintedanib, the anti-VEGF effect may have caused pneumothorax in existing patients with significant fibrosis.

In addition, VEGFR, PDGFRα and FGFR play a role in wound healing; therefore, delayed wound healing may occur in patients receiving nintedanib. There were no reports of prolonged wound healing in the nintedanib group of the SENSCIS study, and there was no difference in the occurrence of skin ulcers as an adverse event between the nintedanib and placebo groups (18.4% and 17.4%, respectively) (3).

The half-life from the steady state of nintedanib 300 mg twice daily is 27.5 hours (6-7). As a result, blood levels of nintedanib are expected to decrease gradually after discontinuation. Nindetanib was not discontinued in the patient's first history of pneumothorax. recurrent pneumothorax may have resulted from adequate reinflation of the lungs after thoracic drainage due to reduced lung compliance. Nintedanib was stopped after surgery.

Hideaki et al. Showed older age and lower BMI were significant predictors of mortality by multivariate Cox regression analysis. ROC analysis showed BMI ≤17.8 kg/m2 to reliably predict poor prognosis (6). However, in our case, the patient was young and had a BMD of 22.

In a case report published from Japan, 2 cases of persistent pneumothorax using nintedanib for SSc-ILD were reported. Similarly, recurrent pneumothorax cases were reported at 14 and 16 weeks after nintedanib 150 mg twice a day.

Conclusion

In summary, although SSc-ILD is a common disease, nintedanib treatment likely increases the risk of resistant pneumothorax. However, we do not currently have sufficient data on this complication. There is a need for case data to be defined in the future.

Conflict of interest: Each author declares that she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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