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Left ventricular dysfunction in an idiopathic pulmonary fibrosis patient on nintedanib

Ryosuke Imai & Yutaka Tomishima

Department of Pulmonary Medicine, Thoracic Center, St. Luke's International Hospital, Tokyo, Japan.

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Correspondence
Ryosuke Imai, Department of Pulmonary Medicine, Thoracic Center, St. Luke's International Hospital, 9-1, Akashi-cho, Chuo City, Tokyo 104-8560, Japan.
E-mail: imai.rysk@gmail.com

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Abstract

Nintedanib, a tyrosine kinase inhibitor, is approved for the treatment of idiopathic pulmonary fibrosis. We report a case of left ventricular dysfunction in a patient with idiopathic pulmonary fibrosis treated with nintedanib, which recovered after cessation of nintedanib. Nintedanib may induce left ventricular dysfunction, and early recognition is important since this condition is potentially reversible.

Introduction

Nintedanib is an intracellular multi-target tyrosine kinase inhibitor (TKI), whose targets include platelet-derived growth factor receptors α and β, vascular endothelial growth factor receptors 1, 2, 3, and fibroblast growth factor receptors 1, 2, and 3 [1]. The use of nintedanib has been demonstrated to significantly reduce disease progression in idiopathic pulmonary fibrosis (IPF) [2] but serious adverse cardiovascular events can occur [3]. We report the first case of left ventricular (LV) dysfunction in a patient with IPF on nintedanib.

Case Report

An 85-year-old Japanese man presented to our clinic with increasing dyspnoea on exertion over 6 months. He had a history of bladder cancer (pT1N0M0, stage IA), in remission at the time of presentation having had transurethral removal of the bladder tumour followed by intravesical Bacillus Calmette-Guerin therapy. He also had a history of hypertension well controlled with amlodipine and candesartan, hypothyroidism treated with levothyroxine, and chronic kidney disease. He was a former smoker with a 27 pack-year history and used to work for a catering company without any specific exposures. He had no previous history of LV dysfunction. On respiratory examination, his SpO_2 was 95% on room air, and he had fine crackles at his lung bases. Cardiac examination was unremarkable with no features of cardiac failure. Chest X-ray showed bilateral reticular changes (Fig. 1A). Chest CT demonstrated changes consistent with a usual interstitial pneumonia pattern, with bilateral reticulation, and minor ground glass opacities with mild honeycombing in both lower bases (Fig. 1C–E). Laboratory testing revealed elevated Krebs von den Lungen-6 level (2117 U/mL, normal 0–500 U/mL). Pulmonary function tests demonstrated a restrictive ventilatory defect with a moderate reduction in gas transfer capacity. Forced vital capacity was 73.9% of predicted and the diffusion capacity of carbon monoxide was 54.5% of predicted.

Auto-antibodies including anti-nuclear antibodies, rheumatoid factor, myositis panel, scleroderma panel, and anti-cyclic citrullinated peptide were negative. The patient was diagnosed with IPF based on the chest computed tomography findings and a negative autoimmune screen in the appropriate clinical setting. He was started on nintedanib 200 mg/day, which was later increased to 300 mg/day. Two months after the initiation of nintedanib, the patient

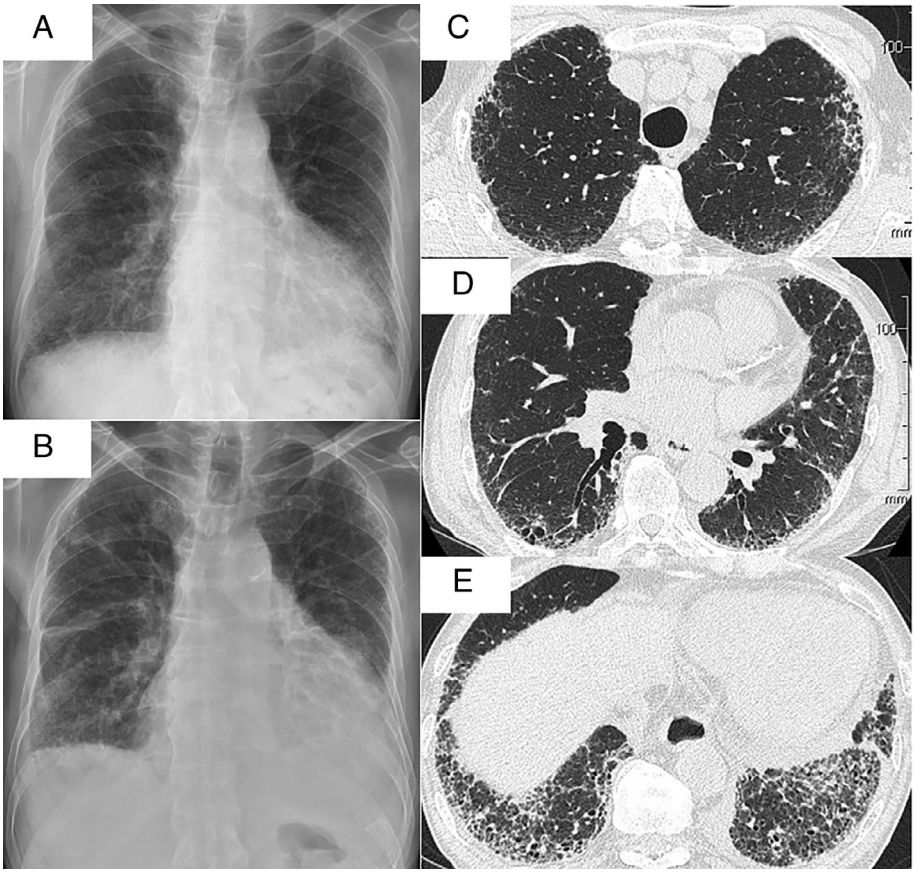

Figure 1. Before nintedanib treatment, chest X-ray demonstrated reticulation, especially in the basal parts of the lung (A). Alveolar oedema developed with cardiac enlargement and bilateral pleural fluid at admission (B). Chest computed tomography showed usual interstitial pneumonia pattern with reticular opacities associated with traction bronchiectasis with peripheral and lower lobe predominance (C–E).

presented to our clinic with a three-day history of dyspnoea at rest and orthopnoea. On examination, blood pressure was 167/58 mmHg, heart rate was 87/min and regular, and he had bilateral pitting oedema in his lower extremities. Laboratory tests revealed no elevation of creatine kinase-MB (14 U/L, normal <30 U/L), mild elevation of troponin T (0.063 ng/mL, normal <0.014 ng/mL) and elevation of N-terminal pro-brain natriuretic peptide (23,908 pg/mL, normal <125 pg/mL). Full blood count was unremarkable, thyroid hormone levels were within normal limits, and a septic screen including laboratory markers of infection was negative. Electrocardiogram showed no ST-T wave changes but a widened QRS-complex (Fig. 2). Chest X-ray showed widespread bilateral infiltrates in the lung fields (Fig. 1B). Transthoracic echocardiogram showed global hypokinesia with an LV ejection fraction (LVEF) of 34% (Video S1), which was 69% before the initiation of nintedanib. Cardiac catheterization revealed no significant coronary stenosis. He was diagnosed with congestive heart failure probably due to nintedanib.

After admission, nintedanib was stopped and furosemide, nitroglycerin, candesartan, and carvedilol were started. The patient improved significantly and was discharged from hospital at day 18. His LVEF recovered to 41% on day 8 of his hospital stay, and to 58% three months after his acute presentation. The patient continues to receive follow-up in the outpatient clinic to monitor LV function and his IPF and he has not experienced heart failure since his discharge.

Discussion

We report a case of an 85-year-old man with LV dysfunction likely caused by nintedanib. The LV function was initially normal, declined after nintedanib treatment, and then improved after cessation of nintedanib and initiation of standard heart failure management. Extensive tests were performed to exclude known causes of heart failure. It has previously been reported that TKIs such as imatinib or sunitinib can cause cardiovascular side effects including heart failure, LV dysfunction, conduction abnormalities, QT prolongation, acute coronary syndromes, myocardial injury, arterial thrombosis, and hypertension [4]. Patients with significant cardiovascular disease were actively excluded from the nintedanib trials in IPF [2] but follow-up of the long-term use of nintedanib in IPF haas

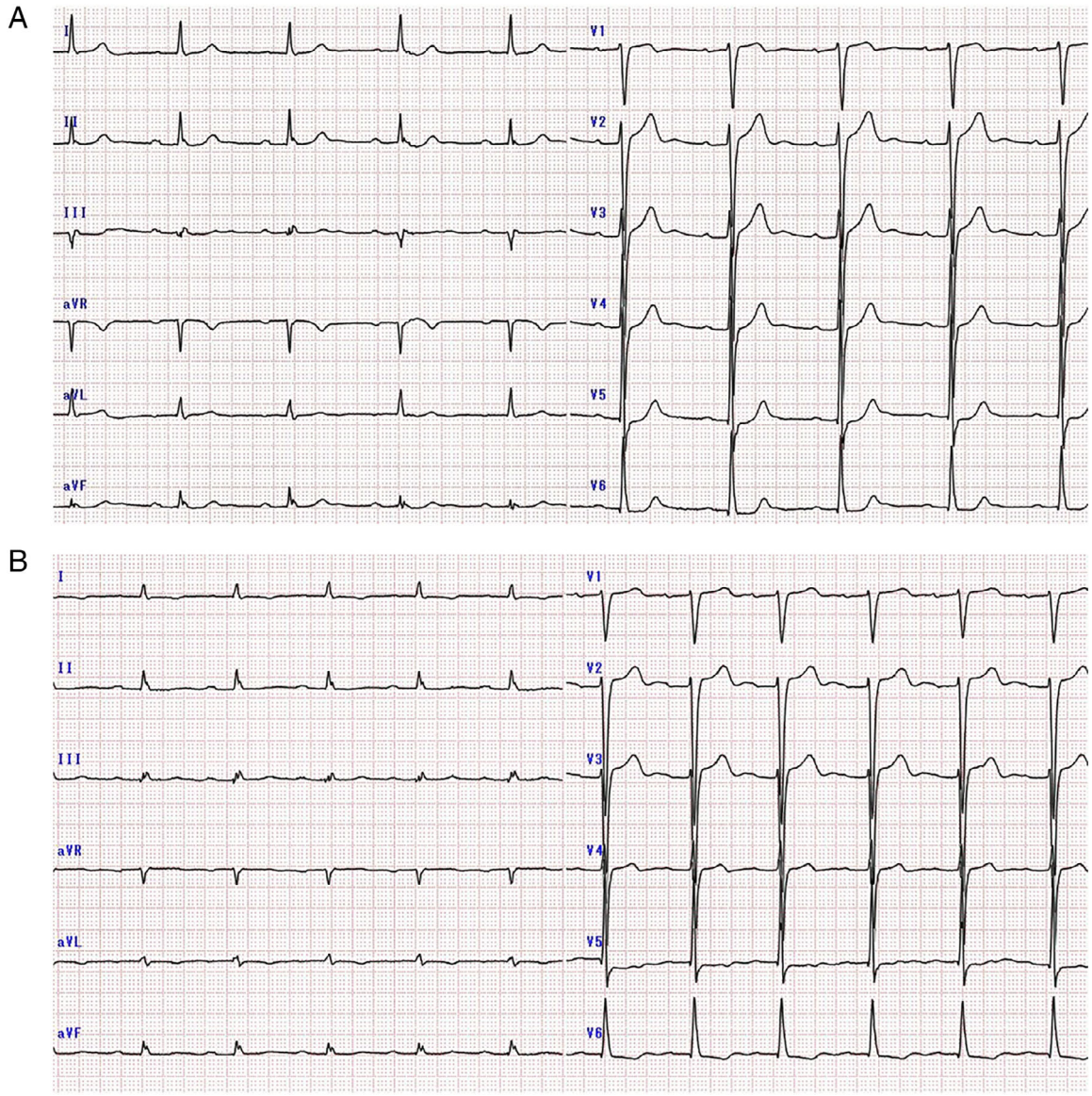

Figure 2. Patient's electrocardiogram before nintedanib treatment (A). It changed in left ventricular systolic dysfunction (B). QRS duration was 116 ms before nintedanib treatment and 124 ms at admission.

been associated with major adverse cardiovascular events in the order of 3.6 events per 100 patient exposure-years [3].

Nintedanib, which is presently approved for the use in IPF, will likely be approved for other forms of fibrotic lung diseases in the future. Therefore, the use of nintedanib will increase over time, warranting further investigation into its clinical and biological effects.

In conclusion, LV dysfunction may develop as an adverse event from the use of nintedanib, and early recognition is important since this condition is potentially reversible upon cessation of the drug.

Disclosure Statement

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

References

1. Richeldi L, Costabel U, Selman M, et al. 2011. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N. Engl. J. Med. 365:1079–1087.

2. Richeldi L, du Bois RM, Raghu G, et al. 2014. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N. Engl. J. Med. 370:2071–2082.
3. Crestani B, Huggins JT, Kaye M, et al. 2019. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. Lancet Respir. Med. 7:60–68.
4. Chen MH, Kerkelä R, and Force T. 2008. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. Circulation 118:84–95.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site: http://onlinelibrary.wiley.com/doi/10.1002/rcr2.533/suppinfo.

Video S1. Parasternal long axis view of echocardiogram obtained at admission showing global hypokinesia with a left ventricular ejection fraction of 34%.