Thrombocytopaenia during nintedanib treatment in a patient with idiopathic pulmonary fibrosis

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Abstract
A 72-year-old Japanese man was diagnosed with idiopathic pulmonary fibrosis (IPF), and treatment with nintedanib was initiated. Ten months after nintedanib treatment initiation, his serum platelet levels gradually decreased until it reached 14,000/mm² and he was admitted to our hospital. At admission, his serum platelet-associated immunoglobulin G level was markedly increased, and bone marrow biopsy showed megakaryocytic hyperplasia. We suspended nintedanib treatment and transfused platelet concentrate. In the absence of evidence of other diseases related to thrombocytopaenia, including Helicobacter pylori infection, thrombocytopaenia was considered to have been caused by nintedanib use. After the patient received high-dose dexamethasone therapy (20 mg/day for four days) and thrombopoietin receptor agonist, eltrombopag olamine (maximum dose: 50 mg/day), the serum platelet count gradually increased. Here, we present a rare case of symptomatic thrombocytopaenia associated with nintedanib treatment in a patient with IPF.

Introduction
Nintedanib is a triple tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor. It is used to treat idiopathic pulmonary fibrosis (IPF) [1,2]. Diarrhoea, nausea, anorexia, and liver dysfunction are the well-known adverse effects of nintedanib. Thrombocytopaenia is a rare adverse effect of nintedanib; thus, there are no reports of frequency of thrombocytopaenia in INPULSIS trial and published case reports of thrombocytopaenia during nintedanib treatment. Herein, we report the first case of thrombocytopaenia during nintedanib treatment.

Case Report
A 72-year-old Japanese man with progressive dyspnoea was diagnosed with IPF two years before this admission based on findings of the usual interstitial pneumonia pattern on high-resolution computed tomography (HRCT) of the chest, and nintedanib treatment (300 mg/day) was initiated one year after the diagnosis. One month after treatment initiation, his serum platelet levels started to decrease (from 263,000 to 176,000/mm², normal: 150,000–250,000/mm²). Eight months after nintedanib initiation, serum platelet levels reached 14,000/mm²; therefore, he was admitted to our hospital owing to haemorrhagic diathesis symptoms. No other diseases or medications were reported before this admission. His laboratory test values on admission were as follows: serum white blood cell (WBC) count 8700/μL (normal: 3590–9560/μL), red blood cell (RBC) count 382 × 10⁴/μL (normal: 400–552 × 10⁴/μL), haemoglobin concentration 12.2 g/dL (normal: 13.2–17.2 g/dL), lactate dehydrogenase 176 IU/L (normal: 119–229 IU/L), sialylated carbohydrate antigen KL-6 642 U/mL (normal: <500 U/mL), and pulmonary surfactant protein-D 131 ng/mL (normal: <110 ng/mL). Serum coagulation factors and d-dimer levels were within the normal range. Serum platelet-associated immunoglobulin G (PA-IgG) level was markedly elevated (2240 ng, normal: <25 ng); other serum autoimmune antibodies tested were unremarkable. Viral serology, including hepatitis (types B and C), cytomegalovirus, and HIV, were negative. No evidence of other haematological diseases was noted in the peripheral serum
examination. Pulmonary function and chest HRCT findings showed no signs of worsening compared to past findings. Abdominal computed tomography (CT) demonstrated no hepatosplenomegaly. Bone marrow biopsy demonstrated megakaryocyte hyperplasia without any findings of malignancy (Fig. 1). The urea breath test indicated possible *Helicobacter pylori* infection; thus, the patient received treatment to eradicate *H. pylori*; however, serum platelet levels did not recover after treatment. Due to the absence of evidence of other diseases related to thrombocytopenia including autoimmune diseases, other haematological diseases, and infectious diseases, we considered that the patient’s thrombocytopenia was due to nintedanib use. Although nintedanib treatment was stopped during admission, there was no increase in serum platelet levels. We administered high-dose dexamethasone (20 mg/day) for four days. After the steroid therapy, the serum platelet levels recovered to within normal range and serum PA-IgG decreased by 120 ng. However, six months after steroid therapy, again, the serum platelet levels decreased and serum PA-IgG levels were increased. We started treatment for thrombocytopenia using eltrombopag olamine, a thrombopoietin receptor agonist. The dosage of eltrombopag olamine was gradually increased every two weeks from 12.5 to 50 mg/day because serum platelet levels decreased with small doses of eltrombopag olamine. Currently, 50 mg/day of eltrombopag olamine is being used as maintenance therapy. After the initiation of these treatments, serum platelet levels recovered and stabilized at approximately 50,000/mm².

**Discussion**

Nintedanib is a triple tyrosine kinase receptor inhibitor [1]; therefore, it is difficult to accurately differentiate between the adverse effects and the inhibition of each receptor. A similar medication, sunitinib, which is a multitarget (VEGFR and PDGFR) inhibitor, is reportedly associated with a high incidence of thrombocytopenia development in renal cell carcinoma patients [3]. In general, drug-induced platelet abnormality was reversed by drug suspension in almost all cases; however, a case of sunitinib-induced prolonged thrombocytopenia despite interruption of sunitinib treatment has been reported [4]. In this publication, a combination of PDGFR and VEGFR inhibition was associated with the development of thrombocytopenia. PDGFR and VEGFR are also inhibited by nintedanib; thus, we consider nintedanib to be the attributable cause of thrombocytopenia in this case.

We considered the association between thrombocytopenia and nintedanib intake due to a few reasons. First, the serum platelet count decreased after nintedanib initiation. Second, there was no evidence of other diseases related to thrombocytopenia, including disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, splenomegaly, or *H. pylori* infection, and no evidence of viral infection. Finally, the patient did not receive any other medications. Although serum platelet levels decreased, serum WBC and RBC levels were normal. Bone marrow biopsy findings were consistent with drug-induced thrombocytopenia according to the lack of evidence of malignancy and presence of megakaryocyte hyperplasia. High serum PA-IgG level is not diagnostic for idiopathic thrombocytopenic purpura (ITP), but it is a known indicator of autoimmunological effects against platelets, including drug-induced effects and those caused by chronic hepatitis and collagen diseases. However, it is impossible to distinguish between ITP and drug-induced thrombocytopenia based on laboratory testing. Therefore, it is important to evaluate clinical cause in association with drug initiation and thrombocytopenia development. Moreover, immune thrombocytopenia induced by drugs has been reported [5]. In our case, thrombocytopenia may have been caused by the development of autoantibodies against platelets, as shown by high levels of PA-IgG.

Long-term prednisolone treatment, dexamethasone pulse therapy, Ig, rituximab, eltrombopag olamine, *H. pylori* eradication, and splenectomy are known treatments for ITP; steroid therapy is the usual first-line treatment. We thought that the pathogenesis of thrombocytopenia in our patient was similar to that of ITP; therefore, we considered steroid administration as the initial treatment for thrombocytopenia. We selected dexamethasone pulse therapy rather than
prednisolone as the first-line treatment of thrombocytopaenia because long-term administration of prednisolone is not recommended in the chronic phase of IPF. Although serum platelet levels temporarily recovered with this intervention, the levels went down again six months after the initiation of dexamethasone. Thus, we decided to change treatment for thrombocytopaenia to thrombopoietin receptor agonists.

In conclusion, we reported a case of symptomatic thrombocytopaenia developed during nintedanib treatment in a patient with IPF. Thrombocytopaenia may result in severe bleeding and can cause a worsened general condition. Although thrombocytopaenia development is a rare adverse effect, clinicians should be aware of the potential platelet decline during nintedanib treatment.

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