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Asymptomatic thrombocytopenia after nintedanib initiation in a patient with progressive pulmonary fibrosis: a case report and review of literature

Xinxin Zhang[1], Zhang Kan[1], Nannan Zhao[1], Na Xi[2] and Tiemei Zhao[1*]

Abstract

Background Nintedanib is a primary antifibrosing medication available for idiopathic pulmonary fibrosis, systemic sclerosis-interstitial lung disease, and progressive pulmonary fibrosis, with scattered report of drug-induced thrombocytopenia.

Case report A 60-year-old Asian male with no history of thrombocytopenia was administered with nintedanib to treat progressive pulmonary fibrosis. The platelet count dropped rapidly after introduction of nintedanib and resolved gradually by withdrawal of the medication along with thrombopoietin receptor agonist.

Conclusion Based on experience from the limited reports, nintedanib-induced thrombocytopenia is typically reversible and manageable. Close monitoring of platelet counts in patients receiving this medication should be warranted.

Keywords Nintedanib, Drug-induced thrombocytopenia, Progressive pulmonary fibrosis, Anti-Mi-2 antibody, Case report

Introduction

Nintedanib is an orally active tyrosine kinase inhibitor that primarily targets platelet-derived growth factor receptors (PDGFRs), fibroblast growth factor receptors (FGFRs), and vascular endothelial growth factor receptors (VEGFRs) [1]. It has noteworthy antifibrotic property and has been approved for treating idiopathic pulmonary fibrosis (IPF), systemic sclerosis-interstitial lung disease (SSc-ILD), and progressive pulmonary fibrosis (PPF). In addition to its antifibrotic effects, nintedanib's inhibition of the aforementioned receptors also disrupts angiogenesis and coagulation processes, leading to bleeding events observed in clinical trials and postmarketing surveillance [2]. Furthermore, nintedanib-induced thrombocytopenia, although rare, has been identified as a potential serious side effect. This study contributes to the limited literature on nintedanib-induced thrombocytopenia by presenting a case of asymptomatic thrombocytopenia that developed shortly after initiating nintedanib treatment, along with a review of similar cases. To our knowledge, it is the first study to report nintedanib-induced thrombocytopenia in patients with an autoimmune feature and diagnosed with PPF.

Case report

A 60-year-old Asian male was admitted due to a productive cough and progressive dyspnea. He was diagnosed with interstitial pneumonia with autoimmune features (IPAF) 4 years ago, presenting with exertional dyspnea,

*Correspondence:
Tiemei Zhao
ztm1111@sina.com
[1] College of Pulmonary and Critical Care Medicine, the 8th Medical Center of Chinese PLA General Hospital, Beijing, China
[2] Department of Pharmacy, Chinese PLA General Hospital, Beijing, China

interstitial pneumonia on computed tomography (CT) scan, and the presence of antinuclear antibodiy (ANA) (1:1000) and anti-Mi-2 antibodies. He had neither skin lesions nor muscle weakness and was tested normal in bilateral thigh muscle magnetic resonance imaging (MRI) scan and electromyography. He had been on long-term corticoid therapy for 2 years with prednisone 5 mg daily. Two months ago, his dyspnea worsened along with a productive cough following an influenza infection. Initial blood tests showed a normal platelet count of 258×10^9/L, elevated white cell count of 10.15×10^9/L, and C-reactive protein of 36.5 mg/L. Procalcitonin (PCT), (1,3)-β-D-glucan and galactomannan testing were negative. Autoimmune tests revealed positive anti-Mi2 antibodies. A CT scan (Fig. 1) indicated increased reticular septal thickening, worsened traction bronchiectasis and newly appeared ground-glass opacities distributed along the bronchovascular bundle and in the subpleural area. Lung function tests demonstrated a decline of 24.1% in forced vital capacity (FVC) compared with the results of 15 months ago. A diagnosis of PPF was confirmed. The corticoid dosage was increased to 20 mg/day of methylprednisolone, and nintedanib 150 mg was administered twice daily, along with ceftriaxone because infection could not be ruled out. Following this treatment, the patient experienced profound alleviation of shortness of breath and cough.

The patient did not have a history of thrombocytopenia and still had a normal platelet count on the fourth day after starting nintedanib. However, the platelet count dropped to 39×10^9/L on the eighth day after nintedanib initiation (Fig. 2). D-dimer and fibrin/fibrinogen degradation products (FDP) levels were normal. Ultrasound examination of the lower-limb veins showed no thrombosis. There were no signs of hepatic cirrhosis or splenomegaly. The most recent influenza infection occurred

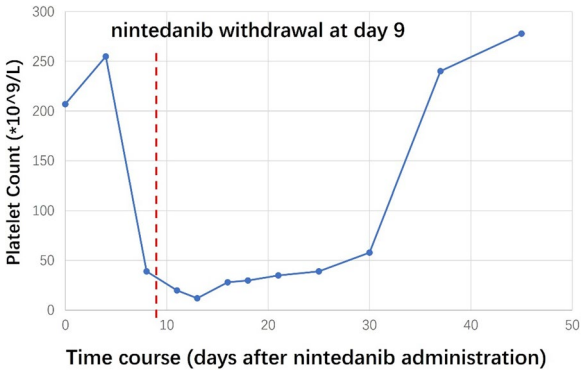

Fig. 2 Platelet count changes since nintedanib initiation

over 2 months before the onset of thrombocytopenia. Concurrent medications, including methylprednisolone, ceftriaxone, and calcium carbonate, did not include commonly known causes of thrombocytopenia. Further examination detected no platelet-specific autoantibodies in the serum.

Nintedanib was suspected to be responsible for the thrombocytopenia and was stopped immediately upon the onset of the latter. The platelet count decreased to 12×10^9/L by the fifth day post withdrawal. A single adult dose of platelets was transfused, and the thrombopoietin receptor agonist, herombopag olamine, was initiated at a dose of 2.5 mg/day. Subsequently, the platelet count gradually increased to 39×10^9/L by the 17th day after discontinuation of nintedanib. Due to the relatively slow rise in platelet count, the dose of hetrombopag olamine was raised to 5 mg/day, leading to an increase in platelet count to 58×10^9/L 3 days later. Following this improvement, the patient was discharged home and continued treatment with herombopag olamine. The platelet count further rose to 240×10^9/L 1 week post discharge and remained stable at a normal level thereafter. Notably,

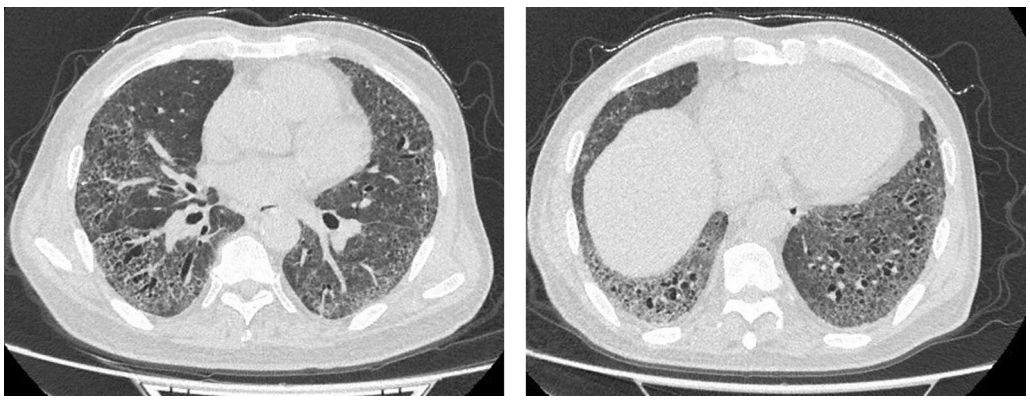

Fig. 1 Chest computed tomography (CT) findings. Reticular septal thickening, worsened traction bronchiectasis, and newly appeared ground-glass opacities distributed along the bronchovascular bundle and in the subpleural area

no bleeding events were observed during the period of thrombocytopenia.

Discussion

Nintedanib, a small-molecule nonselective tyrosine kinase inhibitor, targets key receptors in the pulmonary fibrosis signaling pathway, including vascular endothelial growth factor receptors (VEGFR1-3), platelet-derived growth factor receptors (PDGFRα and β), and fibroblast growth factor receptors (FGFR1-4) [1]. Nintedanib has been approved in over 80 countries for IPF treatment and has shown efficacy in patients with non-IPF interstitial lung disease (ILD) developing PPF. Up to 18–32% of patients with non-IPF ILD are at risk of developing PPF, resulting in rapid decline in lung function, poor life quality, and premature death. Following positive results in the INBUILD trial [3], Nintedanib was authorized for PPF treatment in 2020. Thrombocytopenia, a rare side effect of nintedanib, has been reported in three cases, with varying onset times, as listed in Table 1. A recent report highlighted thrombocytopenia occurring 3 months after nintedanib initiation [4]. In another case study by Ochi *et al.*, a decrease in platelet count was observed 1 month after nintedanib administration [5]. In the present case, thrombocytopenia developed rapidly, with platelet count dropping significantly at the eighth day post nintedanib introduction, consistent with drug-induced thrombocytopenia (DIT) patterns where platelet count typically decreases 5–10 days after drug administration [6]. Patients experienced non-to-mild hemorrhage, potentially influenced by concurrent medications, as seen in a case study by Dumic *et al.*, where a patient taking aspirin exhibited easy bruising despite mild thrombocytopenia [4].

Diagnosing DIT has been a challenging and exclusive process. In this particular case, the possibility of nintedanib-induced thrombocytopenia was considered based on several factors. First, the patient had no previous history of thrombocytopenia, which ruled out congenital conditions such as Fanconi anemia. Second, the serum platelet count decreased upon initiation of nintedanib and increased after its discontinuation, albeit at a slow pace. Additionally, the patient was also taking methylprednisolone, ceftriaxone, and calcium carbonate. Among these, ceftriaxone has been reported to induce thrombotic thrombocytopenic purpura (TTP) in one case [8], while our patient showed no other signs of TTP (normal bilirubin level, no anemia and undisturbed renal function). Besides, the patient received standard dose of ceftriaxone of 2g daily, while retrospective analysis has shown that high dose of ceftriaxone, other than standard dose, was associated with thrombocytopenia [9]. Furthermore, a thorough investigation for other potential acquired causes of thrombocytopenia yielded no evidence of common triggers as illustrated below.

Immune thrombocytopenia can manifest either as a primary condition or secondary to various triggers such as autoimmune diseases, infections, and drugs. In both cases, the presence of antiplatelet specific antibodies is a key characteristic. Primary immune thrombocytopenia is

Table 1 Summary of the reported nintedanib-induced thrombocytopenia cases

Publication year	Patient information	Medical condition	Lowest platelet count ($\times 10^9$/L)	Thrombocytopenia occurring time after nintedanib administration	Duration	With hemorrhage	Treatment	Concomitant anticoagulant/antiplatelet medication
2019 [7]	Not reported	Not reported	25–50	Not reported	Not reported	Not reported	Not reported	Not reported
2020 [5]	Male aged 72	IPF	14	8 months	Persistent	Yes	High-dose dexamethasone; thrombopoietin receptor agonist	No
2023 [4]	Male aged 78	IPF	50–100	12 weeks	3 days	Yes (easy bruising)	Discontinuation of nintedanib	Aspirin
The present report	Male aged 60	PPF	12	8 days	1 month	No	Discontinuation of nintedanib; platelet transfusion; thrombopoietin receptor agonist	No

IPF: idiopathic pulmonary fibrosis; PPF: progressive pulmonary fibrosis

a common cause of low platelet count due to the body's loss of self-tolerance to platelet antigens and abnormal activation of both humoral and cellular immunity, resulting in the presentation of antiplatelet glycoprotein autoantibodies. Secondary immune thrombocytopenia is often seen in autoimmune connective tissue diseases, particularly in systemic lupus erythematosus and primary Sjögren's syndrome (pSS). Thrombocytopenia associated with dermatomyositis is rare and has been minimally reported. A notable portion of these cases have shown positive antiplatelet autoantibodies [10]. Our patient tested positive for anti-Mi2 antibody, a myositis-specific autoantibody, but exhibited no distinct skin lesions or myopathy symptoms and, thus, was not diagnosed as dermatomyositis. Interestingly, the presence of this antibody was detected 3 years prior without any impact on the platelet count. Drugs can induce platelet-specific glycoprotein autoantibodies, and nintedanib may also induce thrombocytopenia in an immune-dependent manner, as demonstrated in the case study by Yusuke Ochi, where a high level of serum PA-IgG was observed, suggesting autoimmunological effects on platelets. But serum tests for platelet-specific glycoprotein autoantibodies were not detected in our patient, hinting a potential nonimmune mechanism underlying the thrombocytopenia.

Thrombocytopenia also occurs following or during many viral infections, with the underlying cause(s) remaining elusive. In this case, influenza infection was speculated as a trigger for exacerbation of interstitial lung disease but not as the direct cause of thrombocytopenia, which occurred 2 months after the infection. Conversely, decrease in platelet count was noted during the acute infection phase of influenza A/H1N1 virus [11]. Other viral infections known to cause thrombocytopenia, such as human immunodeficiency virus (HIV) and hepatitis B/C viruses, were examined and excluded. No evidence of H. pylori infection was observed, and there were no signs of disseminated intravascular coagulation, TTP (as discussed above), or splenomegaly. A bone marrow biopsy was not performed due to the patient's undisturbed white cell and red cell numbers, and the platelet count eventually rose after withdrawal of nintedanib.

Over 300 therapeutic agents have been linked to thrombocytopenia through either immune-mediated or nonimmune-mediated mechanisms [6]. Nonimmune-mediated thrombocytopenia is multifaceted and can result from toxicity-related bone marrow suppression, leading to a decrease in all blood cell lines, from selective impairment in platelet release from megakaryocytes, or from reduced platelet survival in the peripheral circulation. Conversely, drug-induced immune thrombocytopenia involves the development of drug-induced IgG (less commonly IgM/A) that targets and binds to platelet-specific glycoprotein complexes, leading to their destruction via either complement activation and/or phagocytosis [6, 12].

Whether nintedanib induces thrombocytopenia through the suppression of key signaling pathways it targets remains unclear. It is hypothesized that inhibiting PDGFR α and β may impact thrombocyte production. Factors such as stromal-derived factor (SDF)-1 chemokine and FGF-4 have been shown to direct megakaryocytes interactions with the bone marrow stroma and megakaryocyte maturation, with FGF-4, in particular, enhancing megakaryocytes adhesion to marrow endothelium [13].

Withdrawal of the suspected drugs is the initial step in managing drug-induced thrombocytopenia. Typically, platelet count begins to recover after four to five half-lives of the offending drug or its metabolite once treatment is discontinued [6]. In our case, the platelet count continued to decline after withdrawing nintedanib, although at a slower rate, contrasting a previous report where thrombocytopenia resolved promptly within a week of stopping the medication [4]. The exact mechanism is still unknown. The prolonged duration of thrombocytopenia may be attributed to the presence of non-drug-dependent antiplatelet antibodies that persist even after the clearance of the responsible medication. Given the limited sensitivity of antibody-testing methods, it is possible that there is an under-detected immunological effect induced by nintedanib. High-dose corticosteroids and/or IVIG (1 g/kg body weight) are recommended for immune-mediated drug-induced thrombocytopenia to hasten platelet recovery in patients with severe platelet count drops below 50×10^9/L (grades 3 and 4) and bleeding or those at high bleeding risk. Additional therapies such as rituximab or thrombopoietin receptor agonists may be considered for patients not responding to initial treatment [4]. In our case, the thrombopoietin receptor agonist, herombopag olamine, was added as the patient was already on corticosteroid treatment and had a low bleeding risk.

Conclusion

In this study, we presented a case of thrombocytopenia associated with nintedanib administration, highlighting a clear temporal relationship. Our findings suggest that nintedanib-induced thrombocytopenia is typically reversible and manageable, based on the limited reports available. As the use of nintedanib becomes more widespread, it is likely that more cases of thrombocytopenia will be observed. Therefore, we recommend close monitoring of platelet levels in patients receiving nintedanib, particularly those also on anticoagulants and antiplatelet therapy. Further research is needed to elucidate the

mechanisms underlying this rare but potentially serious side effect.

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Author contributions
ZNN and ZK collected the clinical data, and ZXX reviewed the literature and wrote the manuscript. XN contributed in a consultant role and made critical suggestions to address differential diagnoses. ZTM, as senior practitioner of the practice, was responsible for the clinical management of the patient and reviewed the manuscript.

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Availability of supporting data
Data and material supporting this report are available on request from the corresponding author.

Declarations

Ethics approval
Ethical committee approval was not required given the article type.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
All authors have no conflicts to declare.

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