CASE REPORT

Successful Treatment with Edoxaban for Disseminated Intravascular Coagulation in a Case of Aortic Dissection Complicated with Immune Thrombocytopenic Purpura

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Abstract:
A 70-year-old woman was hospitalized for exacerbation of chronic idiopathic thrombocytopenic purpura (ITP) and disseminated intravascular coagulation (DIC) from old aortic dissection. Initially, we increased the dose of prednisolone for ITP. However, her bleeding tendency caused by DIC worsened despite the rapid recovery of her platelet count, and the required amount of fresh-frozen plasma for transfusion increased. The administration of edoxaban for atrial fibrillation led to the marked improvement of her DIC status without serious adverse events. This case suggests that a direct oral anticoagulant may be an effective treatment for DIC caused by aortic dissection.

Key words: edoxaban, direct oral anticoagulant, disseminated intravascular coagulation, aortic dissection

(Intern Med 59: 2035-2039, 2020)
(DOI: 10.2169/internalmedicine.4255-19)

Introduction
Disseminated intravascular coagulation (DIC) is a systemic abnormality causing severe thrombosis and consumption of coagulation factors (1). In particular, DIC induced by vascular diseases, such as aortic dissection or aneurysm, often progresses chronically and is accompanied by severe hemorrhagic complications due to hyperfibrinolysis (2).

While surgical treatment for vascular diseases is frequently performed to improve DIC, it is often difficult for elderly or frail patients to undergo surgery because of its invasiveness. In patients unsuited for surgery, medical treatments have been performed, such as blood transfusion, a combination anticoagulant therapy of heparins and tranexamic acid (3-5), and recombinant thrombomodulin (rTM) (6-9). However, these treatments require long-term hospitalization or frequent hospital visits, which reduce patients’ quality of life.

Direct oral anticoagulants (DOACs) were recently developed and are first-line therapies for nonvalvular atrial fibrillation (NVAF) and deep vein thrombosis. However, the clinical efficacy and safety of DOAC for patients with DIC caused by vascular diseases have not been clarified.

We herein report the effective administration of edoxaban to treat AF in the management of DIC due to aortic dissection.

Case Report
The patient was a 70-year-old woman with a history of artery aortic replacement surgery that was performed for Stanford type A acute aortic dissection in 2011. Subsequently, she had been followed up conservatively. In 2015, she developed petechiae and was diagnosed with idiopathic thrombocytopenic purpura (ITP) at another hospital. She began to receive oral administration of prednisolone (PSL), and her bleeding tendency improved. Therefore, the dose of PSL was tapered, and 5 mg of PSL maintained her platelet count at approximately 100,000/μL.
In April 2018, she consulted a local primary physician with a chief complaint of purpura on her whole body beginning several months prior. Since the platelet count was considerably reduced, she was referred to our hospital. Although atrial fibrillation was found at this time, anticoagulant therapy, such as warfarin, was not started due to her bleeding tendency.

At the time of arrival at the hospital, there was extensive purpura on both extremities (Fig. 1a) and subconjunctival ecchymosis of the left eye. Laboratory measurements showed a low platelet count, consumption of coagulation factors, and active fibrinolysis (platelets 4,000/μL, prothrombin time-international normalized ratio (PT-INR) 1.02, activated partial thromboplastin time (APTT), fibrinogen (Fbg) 89 mg/dL, fibrinogen and fibrin degradation products (FDP) 65.8 μg/mL, D-Dimer 34.8 μg/mL, plasmin-α2 plasmin inhibitor complex (PIC) 21.5 μg/mL, thrombin-antithrombin complex (TAT) 5.6 ng/dL] (Table 1). Platelet-associated IgG (PAIgG) was elevated to 525 ng/10^7 cells (normal range: <46 ng/10^7 cells).

A bone marrow examination showed normocellular marrow, a megakaryocyte count that was within the normal range, and no evidence of hematological malignancy. Computed tomography (CT) revealed a false lumen and mural thrombus in the descending aorta with no evidence of abnormalities other than the aortic dissection, such as hematologic disease, infection, or malignancy (Fig. 2).

Based on her clinical history and the above findings, we diagnosed the patient with both DIC and exacerbation of chronic ITP. The DIC was thought to have been caused by the old aortic dissection. The cause of the exacerbation of chronic ITP, such as prior infection, was unclear.

The clinical course is shown in Fig. 3. Initially, we transfused fresh-frozen plasma (FFP) for hypofibrinogenemia and increased the dose of PSL from 5 to 40 mg (1.0 mg/kg) for ITP on the fourth hospital day. After increasing the PSL dose, her platelet count increased to 117,000/μL in 8 days. Despite the recovery of her platelet count, FDP were elevated, her Fbg level decreased (FDP 144 μg/mL and Fbg 57 mg/dL), and the frequency of FFP blood transfusion in-
While continuing FFP transfusion for DIC, we decided that recommencing therapy for NVAF was also necessary, as her CHA2DS2-VASc score was 3 points (age, sex, and vascular disease). Therefore, we started the oral administration of 30 mg of edoxaban. Edoxaban has dose criteria for patients with renal impairment who are underweight. In this patient, the dose was reduced due to her low body weight. Although mild renal dysfunction was noted, she did not meet the discontinuation criteria.

Figure 2. Enhanced computed tomography on admission. (a-d) Dissection in the descending aorta. The false lumen has blood flow with partial mural thrombus in the thoracic descending aorta.

Figure 3. Clinical course of admission.
DIC subsided a few weeks after the administration of edoxaban (Table 2), and FFP transfusion was no longer needed. During treatment with edoxaban, the purpura also subsided without additional hemorrhaging (Fig. 1b). After we gradually reduced the PSL and confirmed that the platelet count had not decreased, even at 25 mg of PSL, she was discharged after 35 days of hospitalization. At present, the platelet count remains at approximately 100,000 without blood transfusion or a severe bleeding tendency.

### Discussion

The course of this patient suggested two important clinical precepts: edoxaban is useful for DIC due to aortic dissection, and PSL therapy for ITP does not improve the status of DIC.

First, edoxaban can be used to treat DIC. The course of this patient suggested that the administration of edoxaban is useful for DIC due to aortic dissection without severe adverse events. Previous reports of DIC caused by vascular disease have described the effectiveness of rTM (6-9), low-molecular-weight heparin (LMWH) (10-13), nafamostat mesylate (14), and para-aminomethylbenzoic acid (PAMBA) (15). However, the intravenous administration of these drugs places a considerable burden on patients. Therefore, a more convenient therapy, such as an oral agent, is needed. In order to prevent the progress of DIC, excessive coagulation activity must be suppressed. DOACs exert anticoagulant activity by inhibiting Factor Xa (FXa) or thrombin directly. Therefore, in theory, DOACs may contribute to the treatment of DIC. Some reports have described the efficacy of DOACs other than edoxaban, such as rivaroxaban, apixaban, and dabigatran, in treating chronic DIC (11, 16-20). In the present case, we chose edoxaban based on a previous meta-analysis of clinical studies of each DOAC for NVAF (21). According to that report, the hazard ratio of major hemorrhaging as a side effect of edoxaban or apixaban was lower than that for dabigatran or rivaroxaban. Although that report did not allow for a straight comparison due to the different patient backgrounds with each drug, we consider edoxaban to be more effective than rivaroxaban in patients with a strong bleeding tendency, such as the present patient.

To our knowledge, this is the first report to find edoxaban useful for DIC. In Japan, edoxaban is indicated only for patients with NVAF or venous thromboembolism (VTE), making it a promising option for treating DIC patients with such complications. In the future, further studies regarding the clinical efficacy and safety and the adequate dose of edoxaban for DIC caused by vascular diseases will be required. Although warfarin is another anticoagulant, which exerts an anticoagulant effect on vitamin K dependence, it is not recommended for use in the treatment of DIC. As warfarin inhibits substrate coagulation factors, it can promote a bleeding tendency. In AF treatment, there is evidence that the frequency of major bleeding with DOACs is less than that with warfarin (21-24). Therefore, we administered DOAC for the treatment of AF.

Second, in this case, the bleeding tendency of DIC decreased after starting PSL treatment for ITP. There is the possibility that DIC merely deteriorated as part of its natural course, but there may have been other reasons for this progression as well. Previous reports have suggested that corticosteroids reduce the fibrinogen level, although the mechanism underlying this remains unclear (25, 26). Furthermore, corticosteroids are assumed to increase the coagulation activity (27). They cause microvascular endothelial cell apoptosis and suppress endothelial nitric oxide synthase (eNOS), resulting in dysfunction of vascular endothelial cells (27). As endothelial cells use TM, antithrombin, heparinoid, prostaglandin I2 (PGI2), nitric oxide (NO), and tissue plasminogen activator (tPA), this impairment is assumed to lead to hypercoagulation. It has also been reported that steroids cause cell cycle arrest, which prolongs the repair of endothelial cell damage (28). Although this may be one explanation for this progression, there are no clinical reports of corticosteroid effects on DIC to our knowledge. For this reason, whether or not steroids caused the hypercoagulation and deteriorated DIC in the present case is unclear.

In conclusion, edoxaban is an effective treatment strategy for DIC caused by aortic dissection, and PSL can exacerbate the bleeding tendency. Since the adequate dose of edoxaban for DIC is unclear, further investigations are warranted. It is necessary to pay attention to the hypercoagulable status when using corticosteroids for coagulation disorders.

The authors state that they have no Conflict of Interest (COI).
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