Eddyaban was Effective for Treating Renal Vein Thrombosis in a Patient with Nephrotic Syndrome

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Abstract:
A 39-year-old man with nephrotic syndrome was admitted due to right dorsal pain. Contrast-enhanced CT led to a diagnosis of renal vein thrombosis and segmental pulmonary thromboembolism. Treatment with heparin and warfarin was started. After 1 month, pulmonary thromboembolism recurred. Warfarin was switched to edoxaban, and steroid therapy was initiated, which led to the remission of nephrotic syndrome and the disappearance of renal vein thrombosis. The efficacy of edoxaban was demonstrated; however, this drug has not been routinely selected for patients with renal disease. Our results suggest that edoxaban is also effective for treating venous thrombosis patients with nephrotic syndrome.

Key words: edoxaban, renal vein thrombosis, nephrotic syndrome

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Introduction
Nephrotic syndrome is important as an underlying disease that causes venous thrombosis, the presence of which may sometimes influence the prognosis. A hypercoagulable state, which may develop in due to the enhanced synthesis of coagulation factors in the liver, and the loss of coagulation inhibitors may be involved in the pathogenesis of venous thrombosis in patients with nephrotic syndrome. The incidence of thrombosis in patients with nephrotic syndrome may increase with the duration of disease and the severity of hypoalbuminemia (1).

We herein report the case of a patient who developed renal vein thrombosis and pulmonary thromboembolism during the course of nephrotic syndrome and in whom treatment with an oral factor Xa inhibitor (edoxaban) was effective.

Case Report
A 39-year-old man was admitted to our hospital with right dorsal pain in July 2015. Since 2013, health checkups had indicated proteinuria, but he had not undergone a detailed examination due to the absence of symptoms. In July 2015, he consulted a family doctor with right dorsal pain of 2 weeks in duration. Marked proteinuria and hematuria were observed, and he was referred to our hospital. The clinical course of the present patient is shown in Fig. 1.

Dull right dorsal pain and slight edema of the bilateral lower thighs were noted. A physical examination revealed the following findings: blood pressure, 141/100 mmHg; heart rate, 70 beats/min; and respiration 18 breaths/min, respectively. During the past few years, there had been no changes in the patient’s body weight. A urinalysis showed massive proteinuria (5.7 g/day) and hematuria (3+). A blood test indicated hypoalbuminemia (2.6 g/dL) and hypercholesterolemia (TC: 259 mg/dL), which were consistent with a diagnosis of nephrotic syndrome. The serum creatinine level (0.83 mg/dL) was within the normal range. Furthermore, the levels of anti-thrombin III, protein C, protein S, and anti-cardiolipin β2 glycosylphosphatidylinositol (GPI) complex antibodies were measured, but were found to be within the normal ranges.

Ultrasonography showed a shadow defect in the right renal vein, without a blood flow signal. Contrast-enhanced ab-
dominal computed tomography (CT) revealed a shadow defect that involved the entire area of the right renal vein, suggesting renal vein thrombosis (Fig. 2, 3). Contrast-enhanced thoracic CT showed a shadow defect in a portion of the right lower lobe branch, leading to a diagnosis of localized pulmonary thromboembolism. However, ultrasonography did not show deep vein thrombosis of the lower limbs.

The administration of heparin was started on the day of admission. Warfarin administration was initiated on the third day of hospitalization. The patient’s dorsal pain disappeared within a few days, and there were no respiratory symptoms. The proteinuria was stabilized at 3 g/day, and there were no symptoms. The patient was discharged on the 17th day of hospitalization. The presence of diseases that cause thrombosis (other than nephrotic syndrome) was ruled out based on the results of examinations during admission.

Right thoracic pain suddenly occurred at 20 days after discharge, and the patient consulted the emergency outpatient unit of our hospital. At the time, his blood pressure was 142/60 mmHg. Electrocardiography showed arte-
The incidence of venous thrombosis in patients with nephrotic syndrome is reportedly 21–42%, depending on the primary disease and duration of disease (1, 2). In 1840, Rayer reported the association between nephrotic syndrome and renal vein thrombosis for the first time (3). It was initially hypothesized that renal vein thrombosis might cause nephrotic syndrome; however, based on subsequent review, renal vein thrombosis is currently considered to be a complication that occurs in relation to nephrotic syndrome as an underlying disease.

In patients with nephrotic syndrome, the enhancement of glomerular permeability leads to the urinary leakage of various plasma protein components. The levels of coagulation inhibitors, such as anti-thrombin III, also decrease through urinary loss. On the other hand, enhanced protein synthesis in the liver increases the levels of coagulation factors, such as fibrinogen, resulting in a hypercoagulable state. Furthermore, several studies have indicated that endovascular dehydration, long-term recumbency, and the use of drugs, such as diuretics and steroids, were involved in thrombus formation. Thrombus-related clinical symptoms include pain in the acute phase, but chronic thrombosis is asymptomatic in most cases. Thus, there may be many patients with nephrotic syndrome who have latent venous thrombosis that has not been clinically diagnosed. In the present case, dorsal pain initially occurred, suggesting acute renal vein thrombosis. Furthermore, the pulmonary thromboembolism may have been associated with the migration of a small thrombus derived from renal vein thrombosis.

In the 1960s, when a treatment had not been established, the 2-year survival rate in patients with renal vein thrombosis was 22%, due to complications such as pulmonary thromboembolism (4). Anticoagulant therapy is commonly used, with the goal of preventing pulmonary thromboembolism and the recanalization of venous blood flow, to treat venous thrombosis in the presence of nephrotic syndrome. Heparin is administered in the acute phase, then switched to warfarin. As other treatments, some studies have indicated that the administration of urokinase or tissue plasminogen activator (t-PA) was effective (5). As direct treatments for thrombi, thrombectomy with a catheter and intravenous stenting has been reported (6).

Recently, oral factor Xa inhibitors—a new type of drug to replace warfarin—have been used in clinical practice. Several studies have reported the usefulness of these drugs for preventing atrial fibrillation-related cerebral infarction and the prevention/treatment of venous thrombosis (7). However, it is necessary to limit the doses of most drugs in patients with renal dysfunction; few studies have reported the treatment of patients with kidney disease, including those with nephrotic syndrome. With regard to edoxaban, which was administered to the present patient, administration at 30 mg (half the standard dose [60 mg]), is recommended for patients with a creatinine clearance of ≤50 mL/min. Our patient did not meet this criterion; however, edoxaban was administered because his nephrotic syndrome had persisted for a specific period. Although a period of ≥6 months was required, the administration of edoxaban led to the disappearance of renal vein embolism and pulmonary thromboembolism. The most important aim of treatment for venous thrombosis in the presence of nephrotic syndrome is to achieve the remission of nephrotic syndrome as a primary disease. In the present case, remission was maintained by administering a steroid and cyclosporine; however, recrudescence was noted. This may have been the most important background factor for the efficacy of edoxaban therapy.

We reported the case of a patient with nephrotic syndrome in whom an oral factor Xa inhibitor, edoxaban, was effective for treating renal vein embolism and pulmonary thromboembolism. However, oral factor Xa inhibitors must be carefully administered to kidney disease patients. It should be further reviewed whether these can be used as first-choice drugs.

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

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