

# Poor response to rivaroxaban in nephrotic syndrome with acute deep vein thrombosis

## A case report

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### Abstract

**Rationale:** Hypercoagulability can lead to thromboembolic events that are a life-threatening complication of nephrotic syndrome (NS). Conventional anticoagulants are first-line treatment in the presence of demonstrated thrombosis in NS. Direct-acting oral anticoagulants (DOACs) have provided useful alternatives for the prevention and treatment of thromboembolic events.

**Patient concerns:** A 59-year-old male developed lower limbs deep vein thrombosis (DVT) during the early course of NS but presented poor response to oral therapeutic doses of rivaroxaban. The decision was made to switch from rivaroxaban to heparin and subsequently bridged to warfarin. The patient presented significant clinical symptom improvement.

**Diagnosis:** NS with Lower limbs DVT.

**Interventions:** Rivaroxaban was discontinued and switch to heparin and subsequently bridged to warfarin.

**Outcomes:** Venography result of both lower limb vein showed the venous wall was smooth without obvious stenosis or obstruction. Edema of the patient's lower limbs gradually improved and disappeared.

**Lessons:** The existing published data on the application of DOACs in NS are limited. DOACs have an immediate anticoagulant effect and have demonstrated safety and efficacy and required no routine monitoring, however, application of these agents in NS likely requires further investigation before widespread adoption.

**Abbreviations:** APTT = activated partial thromboplastin time, DOACs = direct-acting oral anticoagulants, DVT = deep vein thrombosis, ECT = emission computed tomography, FDP = fibrin/fibrinogen degradation products, INR = prothrombin time-international normalized ratio, LDL = low-density lipoprotein, NS = nephrotic syndrome, PT = prothrombin time, TC = total cholesterol, TG = triglyceride.

**Keywords:** anticoagulation, hypercoagulability, nephrotic syndrome, rivaroxaban

## 1. Introduction

Deep venous thrombosis (DVT) is a significant complication associated with nephrotic syndrome (NS). The incidence of

thromboembolism is approximately 25% in adult patients with NS.<sup>[1]</sup> The exact pathophysiology of thrombogenesis in NS is complex and remains inconclusive. Thrombosis in NS may arise from leakage of high-molecular-weight proteins in addition to albumin leading to a hypercoagulability, increased synthesis of factors promoting thrombosis, platelet activation, and aggregation, activation of the coagulation system (ie, factor V, factor VIII, von Willebrand factor, fibrinogen), or decreased endogenous anticoagulants (ie, antithrombin III, protein C, protein S, tissue factor pathway inhibitor).<sup>[2,3]</sup> Conventional anticoagulants are first-line treatment in the presence of demonstrated thrombosis. Here we report a patient who developed lower limbs DVT during the early course of NS but presented poor treatment on oral therapeutic doses of rivaroxaban.

## 2. Case report

Approval for the study by the local institution review board was not required because it was a case report. The patient provided a written informed consent for the publication of his clinical data. A 59-year-old male was admitted to our hospital with an approximately 12-hour history of swelling pain of left lower limb. Two months previously, he had presented with both lower limbs' edema. Ten days before admission, he had been diagnosed with NS in another hospital but refused a kidney biopsy. Then he was treated with 60mg/day of prednisone and 50mg of dipyridamole 3 times a day. He had a 40-year tobacco history and 10-year erosive gastritis history but no family history of notable illness.

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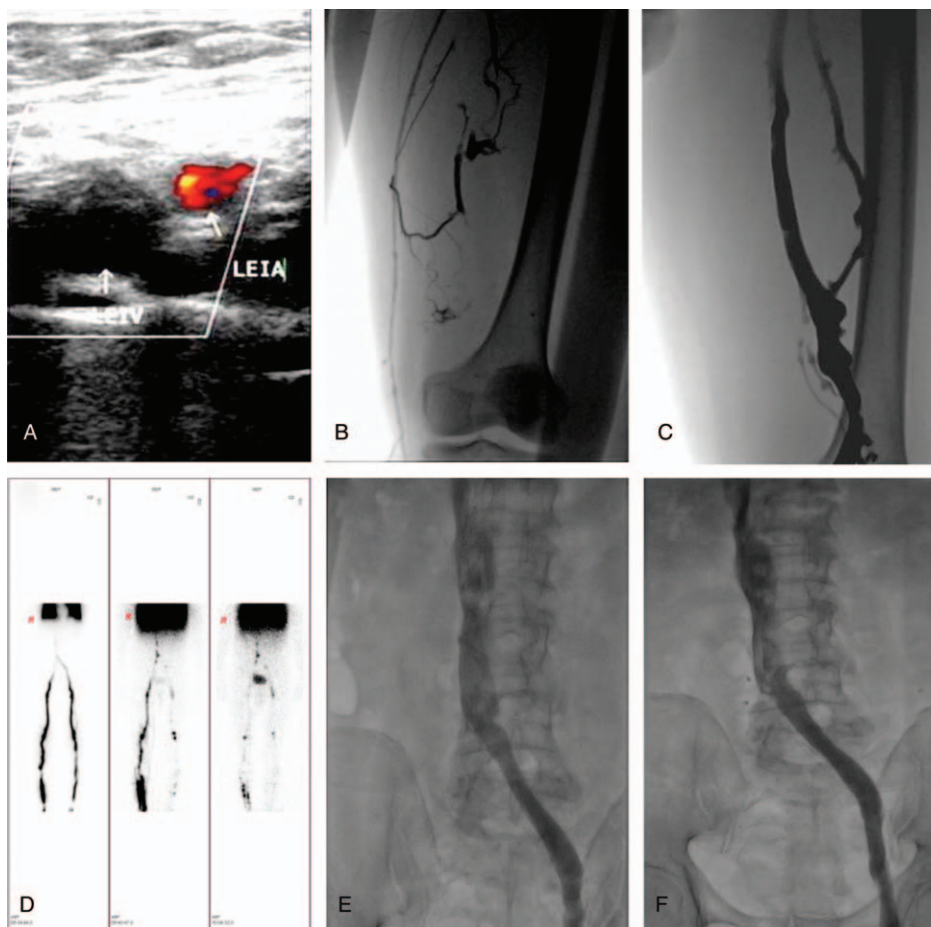
<b>Table 1</b>		
<b>Laboratory test results of the patient.</b>		
	<b>Results</b>	<b>Reference range</b>
Proteinuria	2+	Negative
Urine protein/24 h, mg	2660.0	0.0–150.0
Albumin, g/L	24.5	40.0–55.0
Creatinine, $\mu\text{mol/L}$	75.6	71.0–133.0
TC, mmol/L	10.00	0.00–5.18
TG, mmol/L	2.89	0.00–1.70
LDL-C, mmol/L	6.11	0.00–3.37
D-dimer, mg/L	6.6	0.0–0.3
FDP, $\mu\text{g/mL}$	>150	0.01–5.00
APTT, s	31.3	31.5–43.5
PT, s	14.0	11.0–14.5
INR	1.09	0.70–1.30

APTT=activated partial thromboplastin time, FDP=fibrin/fibrinogen degradation products, INR=international normalized ratio, LDL=low-density lipoprotein, PT=prothrombin time, TC=total cholesterol, TG=triglycerides.

Physical examination on admission revealed the following: height 160 cm, weight 69 kg, blood pressure 130/80 mmHg, heart rate 70 beats/min with a regular rhythm, respiration rate 18/min, and temperature 36.5°C. Left lower limb moderate nonpitting

edema was observed. There was no rash, hyperpigmentation, or anabrosis. The rest of the physical examination was unremarkable.

The patient's laboratory test results are shown in Table 1. Urine sediment analysis revealed massive proteinuria. Twenty-four-hour urine protein excretion was 2660mg. Albumin was significantly lower than normal. The lipid panel revealed total cholesterol, triglyceride, and low-density lipoprotein were high. Initial D-dimer and fibrin/fibrinogen degradation products remarkably increased. Prothrombin time, prothrombin time-international normalized ratio, and activated partial thromboplastin time (APTT) were all normal. Vascular ultrasound showed thrombus of left lower limb vein but no definite abnormality of right lower limb vein (Fig. 1A). And we performed venography of left lower limb vein. The results showed DVT, with total thrombosis of the left common iliac vein and popliteal veins (Fig. 1B). Therefore, we performed balloon dilatation and catheter-directed thrombolysis. And a recyclable inferior vena cava filter was placed. Then thrombolytic therapy with urokinase and anticoagulation therapy with rivaroxaban were initiated. After operation, the patient had a high fever and temperature was 39.2°C. Complete blood count showed white blood cell count  $21.24 \times 10^9$  cells/L, the percent of neutrophil granulocyte 95.3%. Biochemical examination revealed procalcitonin



**Figure 1.** Imageological examination results of the patient. (A) Vascular ultrasound. (B) Venography of left lower limb before thrombolysis and anticoagulation (day 1). (C) Venography of left lower limb after thrombolysis and anticoagulation (day 3). (D) emission computed tomography. (E) Venography of inferior vena cava (day 10); (F) Venography of inferior vena cava (day 15). LEIA=left external iliac artery, LEIV=left external iliac vein.

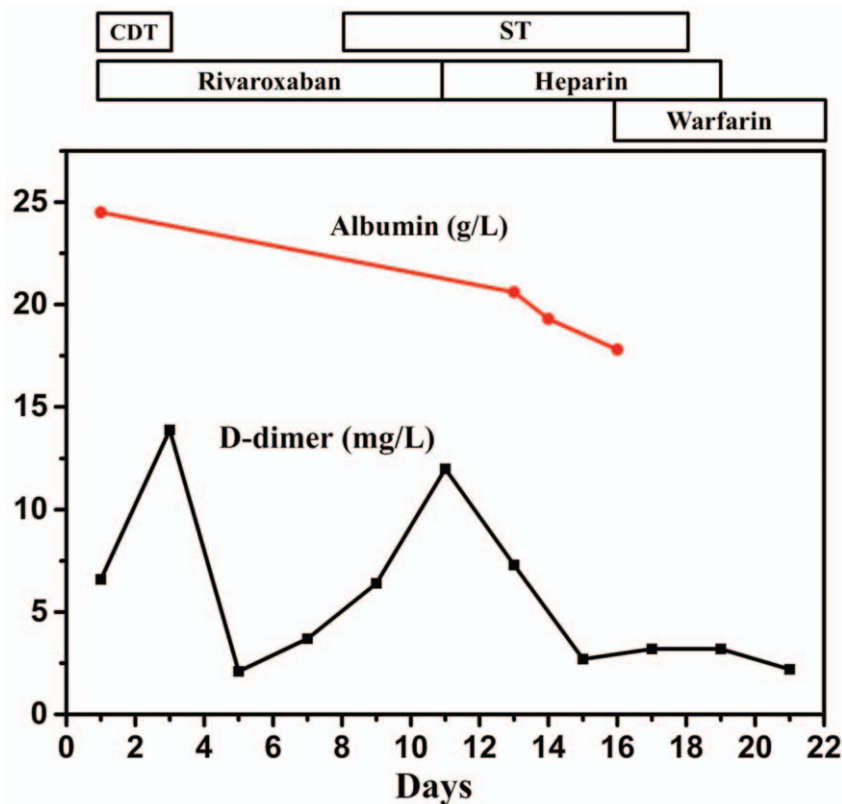


Figure 2. The clinical course. CDT=catheter-directed thrombolysis, ST=systemic thrombolysis.

9.6800 ng/mL. The result of blood culture was *Acinetobacter baumannii*. So antibacterial treatment with meropenem was initiated. On day 3, because the patient was diagnosed with catheter-associated bacterial infection, he removed the thrombolytic catheter and performed iliac vein stent placement. But on day 10, we performed venography of left lower limb vein and inferior vena cava and the results showed thrombosis of inferior vena cava (Fig. 1E). On day 12, emission computed tomography (ECT) examination revealed fresh thrombosis of deep vein in both lower extremities (Fig. 1D). However, bilateral pulmonary perfusion imaging showed no pulmonary embolism. The patient presented no significant clinical symptom improvement and then switched from rivaroxaban to heparin. APTT levels were monitored for dose adjustments so that APTT reached and maintained 1.5 to 2.5 times of normal value. On day 17, venography result of both lower limb vein showed the venous wall was smooth without obvious stenosis or obstruction. Edema of the patient's lower limbs gradually improved and disappeared. The patient was subsequently bridged to warfarin for discharge and continued receiving treatment with glucocorticoids. The clinical course of the patient is shown in Figure 2.

### 3. Discussion

Hypercoagulability associated with NS can lead to arterial and venous thromboembolism. The management of thrombosis in NS is not clearly established because of the lack of large randomized trials and guidelines.<sup>[4]</sup> Conventional anticoagulation remains the standard therapy in the presence of demonstrated thrombosis. At present, the anticoagulants are mainly divided into parenteral

anticoagulants and oral anticoagulants. Parenteral anticoagulants include heparin and low-molecular-weight heparins which bind to and potentiate the effects of antithrombin III.<sup>[5]</sup> Oral anticoagulants include vitamin K antagonists (warfarin) and direct-acting oral anticoagulants (DOACs): direct-acting factors Xa and IIa inhibitors. Warfarin inhibits vitamin K-dependent clotting factors II, VII, IX, and X as well as protein C and S. Owing to its multiple drug and food interactions, the safety, efficacy, and compliance of warfarin have been affected.<sup>[4]</sup> This has prompted the development of DOACs that target key clotting factors Xa and IIa. Rivaroxaban, the first of the DOACs to be FDA approved for both prevention and treatment of venous thromboembolism, is an oral, direct-acting factor Xa inhibitor that is highly protein-bound (90%–95%) in vitro in humans, serum albumin being the main binding component. It is metabolized by CYP3A4 and is the substrate of P-glycoprotein.<sup>[6]</sup> Therefore it may interact with medications that affect these pathways if coadministered. Because of its predictable pharmacokinetic properties, a rapid onset of action, rivaroxaban has fixed dosing and requires no routine coagulation monitoring.<sup>[7]</sup> Although DOACs may simplify thromboembolism prophylaxis in NS and might obviate the need for concern about heparin resistance because of antithrombin urinary losses, whether the pharmacokinetics and pharmacodynamics of these agents are altered in NS is unknown.

In the case reported here, the patient was initially diagnosed with NS and started on conventional corticosteroid therapy with prednisone and antiplatelet therapy with dipyridamole. But DVT occurred 10 days after the diagnosis of NS. Treatment of venous thromboembolism in patients with NS is similar to that in

patients without NS.<sup>[8]</sup> Then thrombolytic therapy with urokinase and anticoagulation therapy with rivaroxaban were adopted. While on anticoagulation with rivaroxaban, ECT examination revealed fresh thrombosis of deep vein in right lower extremities. Venography results showed thrombosis of inferior vena cava. As a result, the patient switched from rivaroxaban to heparin and subsequently bridged to warfarin. In general it is thought that for medications that are highly protein-bound, urinary loss of albumin in NS could lead to higher free drug levels and potential toxicity.<sup>[9]</sup> However it is likely that high protein-binding could lead to urinary losses of the drug. There is a report that high protein-binding of rivaroxaban can lead to increased plasma clearance of the drug in NS which led to treatment failure.<sup>[10]</sup> Or the initial high proportion of free drugs is metabolized and excreted freely, accelerating the release of the binding part and shortening the half-life. This may cause the concentration required for thrombus treatment to fall below the threshold during dosing interval, leading to poor treatment.<sup>[11]</sup> Whether this means that anticoagulation with rivaroxaban in NS requires routine monitoring of serum drug concentrations is uncertain. Compensatory increase in hepatic production secondary to hypoalbuminemia leads to increased activity of clotting factors in NS.<sup>[3]</sup> Rivaroxaban is a direct factor Xa inhibitor. Increased factor levels can make anticoagulants ineffective, which results in treatment failure. Whether this means that the efficacy and bleeding risk of rivaroxaban will depend on the factor Xa levels and whether factor Xa levels should be used to guide anticoagulant therapy in NS are currently unclear. After the admission of 2 days, the patient developed catheter-associated bacterial infection and the result of blood culture was *Acinetobacter baumannii*. Bacterial sepsis induces systemic thrombosis triggered by microbial endotoxin or exotoxin and subsequently releases inflammatory cytokines from monocytes. Hemostatic disorders mediated by tissue factor responses to tumor necrosis factor and interleukin 1 (IL-1) and 6 (IL-6) at the cell surface may lead to hypercoagulability.<sup>[12]</sup> Clinically, significant infection-induced coagulation activation can be observed in 30% to 50% of patients with gram-negative sepsis.<sup>[13]</sup> Hypercoagulability owing to infection in this patient may have increased the difficulty of treatment and prolonged the course of the disease. There is a report that high-dose meropenem inhibits CYP2C19 and CYP3A4.<sup>[14]</sup> So high-dose meropenem can potentially change the exposure of rivaroxaban metabolized by CYP3A4. But this patient was on conventional-dose meropenem; there may be no drug interaction between meropenem and rivaroxaban. Normalization of albumin levels is important because it lowers the level of clotting factors, making anticoagulation more effective. Decreased albumin levels of this patient potentially led to poor treatment during anticoagulation. Therefore, the treatment of NS is crucial to the prevention and treatment of thrombosis.

#### 4. Conclusion

Thromboembolism is a frequent life-threatening complication of NS. Antithrombotic therapy is important in preventing and treating acute and recurrent thromboembolism. We reported the

case of a patient with NS in whom an oral factor Xa inhibitor, rivaroxaban, had poor therapeutic effect in treating acute DVT. Although DOACs have an immediate anticoagulant effect and have demonstrated safety and efficacy and required no routine monitoring, the existing published data on the application of these agents in NS are limited. Many uncertainties remain, such as whether dosing and monitoring should be based on serum factor Xa levels to guide therapy in NS, whether high protein-binding leads to urinary losses of active agent, and whether anticoagulation with rivaroxaban in NS requires routine monitoring of serum drug concentrations. Application of DOACs in NS likely requires further investigation before widespread adoption.

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#### Author contributions

**Data curation:** Yikuan Chen, Xiaotong Qi.

**Writing – review & editing:** Yan Li, Bangqin Hu, Qingqing Du, Yan Qian.

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