Case Report: Possible Rivaroxaban Failure in Patient with Nephrotic Syndrome Discussing Anticoagulation in Nephrotic Syndrome

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Abstract

Kidney disease may cause development of nephrotic syndrome, which is characterized by a variety of factors, including hypoalbuminemia. A well-known complication of nephrotic syndrome is increased risk of Venous Thromboembolism (VTE), caused by various physiologic changes. Multiple treatment options are available for the treatment of VTE, including heparin, warfarin, and non-warfarin oral anticoagulants such as rivaroxaban. In this case report, we describe a 25-year-old male who presented to the Emergency Department (ED) with a Pulmonary Embolism (PE). He was deemed low-risk and eligible for discharge from the ED with rivaroxaban. The treatment is believed to have failed after he developed another VTE in a renal vein five months later while taking rivaroxaban daily. He was admitted to the hospital for thrombolyis and was subsequently diagnosed with nephrotic syndrome and hypoalbuminemia. There is no available data on the use of rivaroxaban in patients with nephrotic syndrome. Despite the fact that hypoalbuminemia could result in higher serum concentration of free drug for highly protein-bound agents such as rivaroxaban, the additional VTE risk inherent to NS appears to have led to re-thrombosis in this patient. Based on the pathophysiology of nephrotic syndrome, we caution the use of rivaroxaban in patients with this condition.

Keywords: Rivaroxaban; Venous thromboembolism; Nephrotic syndrome; Hypoalbuminemia; Pulmonary embolism; Anticoagulation

Introduction

Nephrotic Syndrome (NS) is a rare manifestation of kidney disease with an annual incidence of three per 100,000 persons [1]. NS is defined as proteinuria >3.5 grams per 1.73 m² body surface area per day in association with hypoalbuminemia, peripheral edema, and hypercholesterolemia [2,3]. NS may be caused by systemic disease, medication, infection, or intrinsic renal disease [2].

Development of VTE is a well-known risk of NS with incidence of up to 25% [4]. However, not all causes of NS confer the same risk of VTE. Risk is higher in patients with membranous nephropathy compared to focal segmental glomerulosclerosis and IgA nephropathy [4-6]. A number of physiologic changes occur in patients with NS that may explain the prothrombotic state, which can be generalized as increased platelet reactivity, increased activation of the coagulation system, and reduced activity of the fibrinolytic system [7-9].

VTE includes both Deep Vein Thrombosis (DVT) as well as Pulmonary Embolism (PE). PE may be present in 40% to 50% of patients with DVT and has an average mortality of 10% to 15% in the first one to three months after diagnosis [10-12]. Other complications of DVT and PE include right ventricular dysfunction and post-thrombotic syndrome, which is characterized by pain, heaviness, and swelling of the leg secondary to venous valvular damage caused by the venous thrombus [10].

There are a number of treatments for patients with VTE, including heparin, low molecular weight heparins, vitamin K antagonists (i.e. warfarin), and non-warfarin oral anticoagulants, including factor Xa inhibitors and direct thrombin inhibitors [13]. Of the non-warfarin oral anticoagulants, rivaroxaban, apixaban, edoxaban, and dabigatran are all FDA-approved for treatment of DVT and PE. Rivaroxaban was shown to be a non-inferior treatment option for DVT and PE when compared with the standard of care (i.e. enoxaparin and warfarin.) in the EINSTEIN and EINSTEIN PE trials [14,15]. Rivaroxaban treatment demonstrates unique advantages over traditional therapy with warfarin due to decreased need for laboratory monitoring, dosing adjustments, and decreased costs.
when compared to the standard treatment [16-29]. Rivaroxaban is a highly protein-bound drug with 92% to 95% protein binding (primarily to albumin). It is heptatically metabolized with a terminal half-life of 5 h to 9 h. Approximately 66% of drug excretion occurs in the urine via active tubular secretion [17]. Patients with severely reduced kidney function were excluded from the EINSTEIN and EINSTEIN PE studies; therefore, rivaroxaban should be used with caution in patients with advanced kidney disease [17]. EINSTEIN does not report any demographic or outcomes data in patients with nephrotic syndrome. Clinical management of rivaroxaban in this unique subset of patients remains unclear. This case report describes a recurrence of VTE in a young, previously healthy, obese male receiving rivaroxaban treatment for an unprovoked PE who was later diagnosed with nephrotic syndrome.

Case Presentation

A 25-year-old Hispanic male presented to the emergency department with a chief complaint of chest pain after traveling for approximately 24 h via airplane and car. His past medical history was significant only for obesity, weighing 120 kg with a BMI of 36.8 kg/m² at presentation. There was no known family history of VTE. A chest CT was obtained, which revealed a PE in the subsegmental arteries of the posterior basal right lung. Patient was deemed low-risk based on the absence of Hestia criteria, and discharged with outpatient management [18]. He was prescribed rivaroxaban 15 mg by mouth twice daily for 21 days, followed by rivaroxaban 20 mg by mouth daily for 12 months. Of note, a Comprehensive Metabolic Panel (CMP) upon presentation revealed hypoalbuminemia, with a serum albumin of 3.0 g/dL (normal 3.4 g/dL to 5.0 g/dL). Serum creatinine at that time was 1.06 mg/dL and BUN was 20 mg/dL, both within normal limits.

He followed up with his Primary Care Provider (PCP) two days later and was prescribed tramadol 50 mg and cyclobenzaprine 5 mg for persistent abdominal and chest pain, which was attributed to the recent PE. He also followed up with the outpatient Embolism Clinic, managed by clinical pharmacists, 6 weeks after the PE diagnosis [16]. At this visit, the patient reported no issues with rivaroxaban therapy, indicating no adverse effects or barriers to adherence. He had not missed any doses and the clinical pharmacist verified appropriate fill history with his outpatient pharmacy. Duration of therapy and additional education points were also discussed and documented at that time.

Two months later, the patient presented to the ED with severe abdominal pain and was found to have an extensive right renal vein thrombus that extended into the Inferior Vena Cava (IVC). Of note, the patient was still taking rivaroxaban, as prescribed, at this time. He was noted to have a serum albumin level of 1.8 g/dL.

He was admitted to the hospital, underwent catheter-directed thrombolysis with alteplase and systemic heparin, and a suprarenal IVC filter was placed. Serial imaging showed resolution of caval thrombus with residual non-occlusive renal vein thrombosis, at which point the IVC filter was removed.

Due to developing a new, large thrombus while being therapeutically anticoagulated, Hematology began an inpatient hypercoagulability work-up (Table 1). A scrotal ultrasound and germ cell tumor markers were obtained to rule out malignancy-related VTE; both were normal (Table 2). Nephrology also began to work up and treat his NS empirically with methylprednisolone and prednisone.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 Complement</td>
<td>102 mg/dL</td>
<td>90 to 180 mg/dL</td>
</tr>
<tr>
<td>C4 Complement</td>
<td>9 mg/dL†</td>
<td>10 to 40 mg/dL</td>
</tr>
<tr>
<td>Anti-neutrophil cytoplasmic antibody (ANCA) IgG</td>
<td>&lt;1:20</td>
<td>1:20</td>
</tr>
<tr>
<td>Phospholipase A2 receptor antibody IgG</td>
<td>&lt;1:10</td>
<td>1:10</td>
</tr>
<tr>
<td>Anti-thrombin 3 level</td>
<td>72%†</td>
<td>82% to 136%</td>
</tr>
<tr>
<td>Double Stranded DNA antibody</td>
<td>32 units</td>
<td>0 to 99 units</td>
</tr>
<tr>
<td>Serum alpha-fetoprotein</td>
<td>3.9 ng/mL</td>
<td>0.7-9 ng/mL</td>
</tr>
<tr>
<td>Serum beta-human chorionic gonadotropin</td>
<td>&lt;1 IU/L</td>
<td>0 to 3 IU/L</td>
</tr>
<tr>
<td>Glomerular basement membrane antibody IgG</td>
<td>0 AU/mL</td>
<td>0 to 19 AU/mL</td>
</tr>
<tr>
<td>IgM</td>
<td>40 mg/dL</td>
<td>40 to 230 mg/dL</td>
</tr>
<tr>
<td>IgG</td>
<td>161 mg/dL†</td>
<td>700 to 1600 mg/dL</td>
</tr>
<tr>
<td>IgA</td>
<td>272 mg/dL</td>
<td>70 to 400 mg/dL</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>Normal with all agonists</td>
<td></td>
</tr>
</tbody>
</table>

†Indicates result value outside of the reference range

The decision was made to switch this patient from rivaroxaban to warfarin. He was discharged after 9 days of hospitalization with a 5-day prescription for therapeutic enoxaparin as a bridge to warfarin therapy. The patient has remained on warfarin with no further episodes of VTE to date.

His NS was empirically treated with prednisone until biopsy was done three months after discharge. Immunofluorescence stain for PLA2R and immunoperoxidase stain for TSHD7A, the most common antigens for membranous nephropathy, were both negative at that time [20]. Immunofluorescence stain showed anti-IgG predominant glomerular capillary loop deposits consistent with membranous nephropathy. Electron microscopy also showed numerous subepithelial electron dense deposits, consistent with membranous glomerulopathy. He was started on cyclosporine 100 mg by mouth twice a day, and prednisone was decreased to 40 mg by mouth daily. Immunosuppressive therapy, such as cyclosporine or cyclophosphamide, is indicated in patients with idiopathic membranous glomerulonephropathy who have experienced severe or life-threatening symptoms related to NS [19]. The prednisone dose was tapered and stopped slowly over the following 8 months due to the development of iatrogenic Cushing Syndrome.

Discussion

Thrombus recurrence while therapeutically anticoagulated with rivaroxaban is uncommon [14,15]. The EINSTEINPE trial
demonstrated rivaroxaban treatment provided similar protection against recurrent VTE compared to the standard treatment of enoxaparin bridged to a vitamin K antagonist [15]. However, while patients with creatinine clearance <30 mL/min were excluded, there was no reporting of albumin levels or presence of proteinuria in the study. The clinical conundrum described above raises the question of Rivaroxaban’s efficacy for treatment of PE in patients with NS. There is currently no published data on the efficacy of rivaroxaban in patients with NS or hypoalbuminemia.

Rivaroxaban is a direct factor Xa inhibitor that was approved for the treatment of DVT and PE in 2012. Dabigatran, apixaban, edoxaban, and enoxaparin bridged to a vitamin K antagonist are also approved for the treatment of venous thromboembolism [21]. Rivaroxaban is highly (92% to 95%) bound to plasma protein, the most significant of which is albumin, and has a volume of distribution of approximately 50 liters [17]. It reaches peak concentrations in 2 h to 4 h and has a half-life of 5 h to 9 h in adults and up to 11 h to 13 h in the elderly [17,22]. About 2/3 of each dose undergoes metabolic degradation and about 1/3 undergoes direct renal excretion [17]. Standard dosing for the treatment of DVT or PE is 15 mg by mouth twice a day for 21 days, followed by at least six months of 20 mg by mouth daily.

A number of physiologic changes in patients with NS increase the risk of thrombus formation. Platelets in patients with NS are hypercoagulable, and the degree of hypercoagulability correlates with the severity of NS [23]. This may be due to hypercholesterolemia or increased thromboxane generation [23-25]. Other prothrombotic factors such as factor VIII and fibrinogen also have increased rates of synthesis and increased plasma concentrations in patients with NS [7]. Plasminogen and antithrombin levels are also decreased in patients with NS [7]. These changes all increase the risk of VTE in patients with NS. In addition to NS, the patient was at increased risk for development of VTE due to obesity [26]. However, his hypercoagulability workup by Hematology did not reveal any other definitive causes for increased risk of VTE.

Other physiologic changes in patients with NS could also affect VTE treatment. Urinary protein loss, mostly of albumin but also of other proteins, is a defining feature of NS [2]. Hypoalbuminemia was shown to be an independent risk factor for thrombus formation [27]. Despite this risk, hypoalbuminemia theoretically should increase the serum concentration of free rivaroxaban due to its high degree of protein binding. This juxtaposition of competing factors results in an unclear overall risk profile for thrombus formation. To our knowledge, there are no other case reports or literature evaluating the use of rivaroxaban in patients with NS. Current literature provides the strongest support for the use of heparin or low molecular weight heparins followed by vitamin K antagonist for the treatment of VTE in patients with NS [7,28].

Conclusion

In this case report, we describe a patient with previously undiagnosed NS who developed an extensive renal vein thrombus while being treated for a prior PE with rivaroxaban. Rivaroxaban is one of several drugs approved for the treatment of PE, although limited data exists regarding its use in patients with NS. We suggest that the development of repeat thrombus in this patient may be due to either rivaroxaban treatment failure or the physiologic changes in patients with NS. With numerous alternative treatment options for VTE, we suggest caution in the use of rivaroxaban in patients with NS. The patient described herein has been successfully managed to date with warfarin.

References


