Venous thromboembolism - An unusual case of treatment resistance

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Received - 01 January 2020 Initial Review - 22 January 2020 Accepted - 03 February 2020

ABSTRACT

Nephrotic syndrome (NS) is associated with a hypercoagulable state and hence a serious risk of thromboembolism. Diagnostic and anticoagulation-related management strategies are controversial in NS. We report the case of a 32-year-old young male presenting with deep vein thrombosis (DVT) who on evaluation, was diagnosed with NS. Despite several days of standard medical therapy with low-molecular-weight heparin and warfarin and surgical intervention, clinical response was lacking. However, a dramatic improvement was observed after initiation of rivaroxaban therapy, with complete resolution of DVT in 2 weeks.

Key words: *Nephrotic syndrome, Rivaroxaban, Venous thromboembolism*

Venous thromboembolism (VTE), which encompasses both deep vein thrombosis (DVT) and pulmonary embolism, is a common medical disorder with an annual worldwide incidence of 1–2/1000 population [1,2]. Prothrombotic states, immobility, and systemic malignancies are the major etiological factors for VTE. Standard management of VTE comprises of an initial course of heparin along with oral Vitamin K antagonist (VKA) overlap and continuation [3]. This therapy is proven to be effective; however, it requires frequent laboratory monitoring of prothrombin time and dose adjustments to maintain international normalized ratio (INR) in the therapeutic range. However, this standard therapy may not be effective in certain clinical situations. Newer oral anticoagulants may play a pivotal role in the treatment of such cases.

CASE REPORT

A 32-year-old male presented with a 5-day history of pain and swelling of his right leg. He also complained of pedal edema and passing turbid, frothy urine for the preceding 6 months. There was no history of facial puffiness, oliguria, fever, hematuria, dyspnea, or any other thrombotic episode in the past.

On evaluation, he had a pulse of 92/min and regular, blood pressure of 116/72 mmHg. There was pitting pedal edema up to mid-shin level. His right leg was swollen, and calf tenderness was noted. There were no other local signs to suggest inflammation. The rest of the general and systemic examination was normal.

His hemogram was normal. Urine analysis revealed proteinuria, 2+ by dipstick, and 24 h estimation of 2361 mg. The urine protein-creatinine ratio was 11:1. His metabolic panel was as follows: Serum albumin 1.9 g%, serum creatinine 1 mg%, total cholesterol 380 mg%, triglycerides 157 mg%, and low-density lipoprotein 278 mg%. Venous Doppler demonstrated DVT involving the right common femoral, external iliac, common iliac veins, and lower inferior vena cava (IVC). Sonologically, normal kidneys were noted on ultrasound.

After admission, standard therapy with low-molecular-weight heparin and warfarin (oral VKA) was initiated. However, no clinical response was noted despite 5 days of therapy. Autoimmune and thrombophilia workup was carried out while the patient was on anticoagulation. Anti-nuclear antibody and anti-phospholipid antibody tests were negative, serum homocysteine levels were normal. Protein C, S, and antithrombin 3 (AT3) activities were not measured.

On the day of admission, the patient underwent catheter-directed thrombolysis (CDT) with urokinase through popliteal vein alongside heparin infusion with activated partial thromboplastin time monitoring. Check venograms were obtained at 0, 24, 48, 72, and 84 h of the procedure. After 72 h, a suboptimal response was noted despite continuous urokinase infusion with no improvement in venous flow or leg swelling. The patient was subjected to venoplasty of the common and external iliac vein with iliac vein stenting. At 84 h, check venogram revealed stent occlusion with thrombus.

In view of strong clinical suspicion of nephrotic syndrome (NS) and normal creatinine clearance, the decision to start rivaroxaban (oral Factor Xa inhibitor) was taken. The patient showed a dramatic clinical response with a marked decrease in the leg swelling and pain. He was gradually ambulated. He was discharged with rivaroxaban at initial doses of 15 mg BD for 21 days followed by 20 mg once a day (OD). Nephrologist opinion was sought and the patient was started on therapy with

frusemide, ramipril, statin, folate, and protein supplements. At follow-up on day 15, a total resolution of DVT was seen on check venogram.

DISCUSSION

Pulmonary thromboembolism (PTE) is a very common and potentially fatal disease. An accurate clinical diagnosis must be established and effective treatment administered to prevent complications and improve prognosis [4].

Iliofemoral DVT is defined as thrombus involving the iliac and/or common femoral veins with or without extension into IVC, representing 25% of all DVT [5]. It has higher risks of adverse outcomes such as leg pain, ischemia of limb, and recurrent pulmonary embolism as compared to femoropopliteal or distal DVT [4,6]. As these poor outcomes are seen with standard anticoagulant therapy, a trial of strategies to reduce or clear thrombi such as thrombolysis [7,8], CDT [9], and surgical thrombectomy [4,6] has resulted in improved outcomes as compared to anticoagulation alone. These procedures are resource intensive, have associated potential complications and not uniformly available [10]. These modalities may be indicated if the patient is unresponsive to acute anticoagulation such as the presence of severe disease [10].

Studies show that patients with NS, both hospitalized and ambulatory, have 3–35 % risk of thromboembolic events [11,12]. Hypercoagulability in NS is mainly attributed to decreased AT3 due to urinary loss which is seen in around 86.4% of patients with NS [11]. A state of hypercoagulability and risk of thromboembolism, in both arterial and venous circulation, is a relatively frequent feature of NS in both adults and children [2]. The anticoagulant action of heparin is dependent on adequate circulating levels of AT3. As AT3 production and consumption is a dynamic process, in the setting of reduced AT3 activity levels, heparin-mediated thrombin inhibition is lacking causing a decreased heparin sensitivity [13,14] which is termed as heparin resistance or heparin tachyphylaxis. This state causes insufficient anticoagulation during the initial phase of acute thromboembolism, causing treatment failure [14].

Li *et al*. reported a 3.5 month mean duration for the presentation of venous thrombosis in patients diagnosed with NS with membranous nephropathy [12]. The risk of thrombotic events is the maximum in the initial months of diagnosis of NS; hence, expert recommendation is to use prophylactic anticoagulation within the first 6 months. In addition to NS, AT3 deficiency states could be inherited or acquired due to liver cirrhosis, protein-losing enteropathy, sepsis, polytrauma, hepatic vein occlusive disease, and metastatic tumors [15]. The standard therapy for DVT and PE is iv/sc heparin and oral VKA such as warfarin.

With several practical advantages over this standard therapy, direct oral anticoagulants (DOACs) are fast emerging as novel treatment options for DVT management. Recent research suggests that DOACs which target Factor Xa have comparable efficacy as that of warfarin and with much favorable safety profile. The function of DOACs drug, rivaroxaban which is an oral Factor Xa inhibitor, is independent of AT3, hence, may be superior to heparin as a choice of treatment for AT3 deficiency states such as those with NS. Rivaroxaban may present a simple fixed-dose regimen for DVT treatment without laboratory monitoring [16].

Dupree and Reddy reported a case of an 18-year-old female patient with NS with renal vein thrombosis with PTE despite being on therapeutic doses of warfarin with INR 2–3 goal, who responded to rivaroxaban, a target-specific oral anticoagulant. The efficacy of rivaroxaban as compared to warfarin could be due to its predictable pharmacokinetic profile and lack of requirement of routine monitoring [6]. Yamaguchi *et al*. reported a case of successful treatment of massive PE using rivaroxaban in a patient with AT3 deficiency [17]. Many studies demonstrate comparable safety and efficacy of DOACs as compared to warfarin due to stable pharmacodynamics and pharmacokinetics [17]. Einstein study showed safety and efficacy of Rivaroxaban [17]. However, it did not evaluate patients with hemodynamic instability and those requiring thrombolysis. Rivaroxaban does not seem to have any demonstrable effect on AT3 activity [17].

CONCLUSION

Rivaroxaban being an oral direct Factor Xa inhibitor has a superior therapeutic effect as compared to traditional anticoagulants and functions independent of AT3 levels in serum. Compliance is also better due to fixed-dose oral regimen as opposed to heparin injections and non-requirement of laboratory monitoring. Renal dysfunction is a contraindication for the use of DOACs.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Nilajkar G, Naik M, Sambhaji C. Venous thromboembolism - An unusual case of treatment resistance. Indian J Case Reports. 2020;6(2):64-66.

https://doi.org/10.32677/IJCR.2020.v06.i02.007