Direct oral anticoagulant successfully used to treat an adult nephrotic patient complicated with portal vein thrombosis

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Abstract

Thromboembolism is a major complication of nephrotic syndrome, with the renal vein being the most frequent site. However, the incidence of portal vein thrombosis (PVT) in patients with nephrotic syndrome is rare. We report a case of a relapsed steroid-dependent minimal change disease with incidental PVT. A 38-year-old man presented with anasarca. Elevated liver enzymes were discovered during routine blood testing within days after commencing treatment. Although drug-induced liver injuries are frequently observed with mild aminotransferase abnormality during therapy with steroid or immune-suppressive agents, imaging revealed a massive thrombus of the portal vein, which was treated by anticoagulant therapy with edoxaban. Treatment with anticoagulant therapy could normalize liver function. Two months after the initiation of treatment with edoxaban, the follow-up CT scan and ultrasound showed the disappearance of PVT. Our case suggests that much attention should be paid to PVT as a cause of liver enzyme elevation when treating patients with nephrotic syndrome.

Keywords Nephrotic syndrome · Portal vein thrombosis · Liver enzyme elevation · Direct oral anticoagulant

Introduction

There is general agreement that venous thromboses occur only when several factors are combined [1]. These factors comprise inherited or acquired prothrombotic disorders, other thrombophilic factors, and local factors. Nephrotic syndrome (NS) is associated with hypercoagulable states and a subsequent high risk of venous and rarely arterial thromboembolism. The pathophysiology of thrombogenesis is not well-understood and the risk factor of thrombotic events in patients with NS is characterized by age, histologic type of renal disease, urine protein excretion, and level of serum albumin [2]. Portal vein thrombosis (PVT) is also associated with a thrombophilic condition such as thrombocytosis and platelet hyperaggregability, antithrombin III, plasminogen, protein C, and protein S deficiency, or factors V and VIII increase [3–5].

The most common sites of thrombosis during NS are small veins or small arteries. Although the frequency of arterial thrombosis is much lower compared to venous thromboembolism (VTE), arterial thrombosis can be critical and one of the major life-threatening complications of NS [6]. VTE in adult nephrotic patients involves deep venous thrombosis, renal vein thrombosis, and pulmonary embolism. Other common sites of VTE that have been mainly reported in children include portal vein, splenic vein, internal jugular vein, cerebral venous sinuses, and vena cava [2]. PVT in adult NS is rare and a diagnosis for PVT is delayed in many cases because of its nonspecific presentations. Here, we report a case of portal vein thrombosis which occurred in a male patient with a relapsed steroid-dependent minimal change disease (MCD), and who was successfully treated with anticoagulation therapy.

Case report

A 38-year-old man was referred to our hospital for an evaluation of NS from a community hospital. Three weeks prior to the first visit, he developed anasarca with a body

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weight gain of 14 kg. He was diagnosed with MCD by renal biopsy. He had been treated with corticosteroid and then the treatment was discontinued when complete remission was achieved. He was followed up regularly in our hospital. Four years later, he was hospitalized because of bilateral lower leg edema again.

On physical examination, his body temperature was 36.1 °C, blood pressure 121/77 mmHg, respiratory rate 20 breaths/min, and heart rate 84 beats/min. He gained weight of about 10 kg in 1 month. Initial laboratory data showed a relapse of NS. Total protein was 3.7 g/dL and serum albumin was 1.3 g/dL. His total cholesterol was 391 mg/dL. The spot urine protein creatinine ratio was 15.1 g/gCr. The blood urea nitrogen was 12.0 mg/dL and creatinine was 0.73 mg/dL. Because the clinical presentation was suspected of recurrence NS, steroid pulse therapy was started at a dose of 1 g/day methylprednisolone for 3 days followed by oral administration of 45 mg of prednisolone. On day 19, AST and ALT were raised to twice the upper limits of normal and γ -GTP reached

910 U/L (Table 1). Abdominal ultrasonography was performed and showed ascites, and an extensive thrombus of the portal vein (Fig. 1). Enhanced abdomen computed tomography (CT) scan confirmed the presence of PVT (Fig. 1). There were no abnormalities in kidneys, liver, renal veins, inferior vena cava, and sub-hepatic veins. We evaluated the coagulation components with prothrombin time, activated partial thromboplastin time, protein C, protein S, and antithrombin III. His prothrombin time was 10.3 s, INR 0.85 (international normalized ratio, normal range: 0.85–1.15), the activated partial thromboplastin time was 26.6 s (normal range: 24.3–35.0), and the antithrombin III was 94.2% (normal range: 71–115%). Protein C showed 214% (normal range: 62–131%) and protein S 82% (normal range: 74–132%) (Table 1). From these clinical data, we ruled out the causes other than nephrotic syndrome, including myeloproliferative disease, antiphospholipid syndrome, and connective tissue diseases. Therefore, anticoagulant therapy with edoxaban (30 mg p.o. per day) was initiated immediately. Two

Table 1 Laboratory data at admission and at onset of PVT

Laboratory test					
Peripheral blood		Chemical analysis		Blood coagulation	
WBC	11,400/mL	Amy	72 U/L	PT	10.3 s
Seg.	92.0%	T-Cho	391 mg/dL	APTT	26.6 s
Lymph.	5.0%	HDL-Cho	122 mg/dL	Fib	579 mg/dL
Mono.	2.0%	TG	157 mg/dL	FDP	33 μ g/mL
Eos.	1.0%	Blood sugar	148 mg/dL	D-dimer	23.8 μ g/mL
RBC	535×10^4 /mL	HbA1c (NGSP)	6.3%	ATIII	94.2%
Hb	16.1 g/dL	Serology		Protein C	214%
Ht	48.0%	CRP	0.05 mg/dL	Protein S	82%
Plt	29.1×10^3 /mL	IgG	357 mg/dL	Urinalysis	
Chemical analysis		IgM	54 mg/dL	PH	7.5
AST	20 U/L	FT3	2.3 pg/mL	Protein	4+
ALT	20 U/L	FT4	1.02 ng/dL	Occult blood	2+
LDH	227 U/L	TSH	0.5 μ U/mL	Sugar	-
γ GTP	74 U/L	AFP	8 ng/mL	Sediment RBC	10-19/HPF
ALP	191 U/L	PIVKA-II	37 mAU/mL	WBC	0-1/HPF
T-bil	0.7 mg/dL	CEA	1.6 ng/mL	RBC cast	0/LPF
TP	3.7 g/dL	CA19-9	52 U/mL	Granular cast	0/LPF
Albumin	1.5 g/dL	ANA	Negative	Fatty cast	0/LPF
Uric acid	4.9 mg/dL	aCL	Negative	Urine chemistry	
BUN	12 mg/dL	β 2GPI	Negative	Protein	738 mg/dL
Creatinine	0.73 mg/dL	Syphilis (RPR) (TP)	Negative	Creatinine	48.8 mg/dL
Na	142 mg/dL	HBs Ag	Negative		
K	4.5 mg/dL	HBs Ab	Negative		
Cl	108 mg/dL	HBs Ab	Negative		
Ca	7.2 mg/dL	HBs Ab	Negative		
IP	3.6 mg/dL				

Laboratory results obtained at admission except for the coagulation and fibrinolytic data obtained at onset of PVT

Fig. 1 The initial abdominal ultrasonography and computed tomography (CT). **a, b** Acute portal vein thrombosis in main stem and segment branches. **c, d** Enhanced abdominal CT scan showed thrombosis in both the branch and trunk of the portal vein

months later, complete remission (reduction of proteinuria to < 300 mg/day) of the NS was achieved and the follow-up CT scan and ultrasound showed progressive disappearance of PVT (Fig. 2). Based on this result, we discontinued the therapy with edoxaban. After that, we

have continuously checked to confirm that there are no problems with venous thromboses by routine ultrasound screening.

Fig. 2 The follow-up abdominal ultrasonography. **a, b** Follow-up abdominal ultrasonography 8 months after the onset of portal vein thrombosis. There is no evidence of thrombi in portal vein, suggesting resolution of portal vein thrombosis after complete remission was achieved

Discussion

The incidence of PVT among patients without cirrhosis is unclear. Venous thrombosis is recognized as a major complication of nephrotic syndrome. However, there are few reports regarding PVT [6]. In the present case, in the context of proteinuria and hypoalbuminemia, the patient relapsed to NS. Kidney biopsy performed 4 years ago showed characteristic morphology of MCD and a definitive diagnosis of MCD was made. Methylprednisolone pulse therapy resulted in a rapid response, followed by an improvement of proteinuria. The patient achieved complete remission of NS. However, his history of NS and elevated serum levels of hepatic enzymes led us to suspect not only drug-induced liver injury but also thrombosis of the hepatic portal venous system.

PVT is basically defined as a condition resulting from formation of a blood clot in the extrahepatic portion of the portal vein and is a multifactorial process, in which local inflammatory foci and systemic prothrombotic factors concur. In our patient, extensive biochemical screening and imaging tests failed to find common causes of PVT such as liver disorder, thromboembolic diseases, malignancies, intra-abdominal infections or trauma. In the process of treatment for NS, diuretic therapy for controlling the anasarca, continued use of glucocorticoids, and immobilization during hospitalization seemed to have played an important role in the pathogenesis of PVT. In addition, PVT is classified into acute PVT and chronic PVT. Acute PVT is considered when symptoms develop < 60 days before clinical presentation, and there is no clinical, radiological, or collateral circulation or endoscopic evidence of portal hypertension. Patients with acute PVT might manifest with vomiting, abdominal pain, anorexia, fever, diarrhea, nausea or distension [7]. However, Primignani et al. showed that the acute events possibly are asymptomatic or characterized by nonspecific symptoms as is the case of our patient [8]. It is very difficult to accurately diagnose PVT in patients with NS.

In addition, the aims of therapy for acute PVT consist of resolution of symptoms, complete patency of the portal vein, prevention and treatment of mesenteric ischemia, prevention of chronic PVT development, and prevention of thrombus extension. Literature is scarce regarding PVT, and there are no randomized controlled studies on the efficacy of most forms of therapy for it. Treatment currently includes treating the underlying etiology of NS, as well as anticoagulation, thrombolytic therapy, thrombectomy, and transjugular intrahepatic portosystemic shunt (TIPS) placement. Anticoagulation is usually the common approach to the use of unfractionated heparin, synthetic

polysaccharides, or low molecular weight heparin (LMWH) such as enoxaparin or dalteparin and followed by warfarin using a target INR of 2–3. Anticoagulation therapy is a safe and effective method for patients with symptomatic acute PVT. However, unfractionated heparin requires the use of an inpatient laboratory monitoring and has the risk of heparin-induced thrombocytopenia and osteoporosis [9]. Warfarin is also associated with a high risk of hemorrhage, since some of patients with severe liver insufficiency as in our case have baseline elevated INR levels and INR has only been validated in individuals with normal liver functions. In addition, it is difficult to maintain a therapeutic range of INR in these patients due to a fragile hemostatic environment [10]. LMWH has been suggested as a safe and effective modality for the anticoagulant of choice, but it can be difficult to administer with concerns of distribution in patients with anasarca and ascites, since absorption subcutaneously might not be adequate in sites with interstitial edema [11].

Recently, direct oral anticoagulants (DOACs) such as apixaban, dabigatran, rivaroxaban, and edoxaban are approved for use in prevention or treatment of stroke, VTE, and PE. Our case is the first report in which edoxaban has been able to successfully treat acute PVT during adult NS. The American College of Chest Physicians (ACCP) and American Association for the Study of Liver Disease (AASLD) clinical guidelines suggest DOACs are generally not recommended due to a lack of large-scale studies and the absence of clinical experience with the use of DOACs [12, 13]. The decision whether to treat or not should be based on the potential benefits and risks of the therapy. The newer generation of DOACs is associated with good efficacy safety profiles without coagulation monitoring. A very recent report suggested that newer oral anticoagulants are safe and efficacious alternatives to traditional anticoagulation with low molecular weight heparin and vitamin K antagonists in the treatment of acute portal vein thrombosis with or without cirrhosis [14]. However, there is little data for evaluating the safety and efficacy of the treatments in PVT patients with liver insufficiency and NS. We chose edoxaban for this patient who is likely to have a relapse of NS with VTE, because edoxaban is one of the DOACs and only an approved anticoagulant for preventive administration. Our experience with this patient leads us to believe that DOACs therapy is a useful alternative treatment for the management of PVT during adult NS. A major concern is the lack of long-term studies on patient outcomes after treatment of DOACs. Further studies with more patients such as prospective cohort studies and randomized clinical data should be carried out to determine the true benefit of this therapy.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human and animal rights This article contains no studies involving humans or animals.

Informed consent Informed consent was obtained from the patient whose case is reported in this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB Approval Number 680-2) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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