Retroperitoneal Bleeding: An Experience During Prophylactic Anticoagulation in a Patient With Nephrotic Syndrome

Clinical Medicine Insights: Case Reports
Volume 10: 1–5

DOI: 10.1177/1179547617723317

Mari Okada[1], Tetsu Akimoto[1], Mutsumi Kawamata[1], Toshimi Imai[1], Erika Hishida[1], Marina Kohara[1], Atsushi Miki[1], Takuya Murakami[1], Taro Sugase[1], Takahiro Masuda[1], Yuko Ono[2], Yoshihiko Ueda[2], Osamu Saito[1], Shigeaki Muto[1] and Daisuke Nagata[1]

[1]Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Shimotsuke-Shi, Japan. [2]Department of Diagnostic Pathology, Dokkyo Medical University Koshigaya Hospital, Saitama, Japan.

ABSTRACT: The association between nephrotic syndrome (NS) and a hypercoagulable state has been demonstrated. Controlling the blood clotting activity may therefore be attractive for patients with nephrosis in terms of thromboembolism prophylaxis. We herein report a 75-year-old woman with minimal change disease who developed pains in the right back, groin, and thigh because of retroperitoneal bleeding during prophylactic anticoagulation with unfractionated heparin. Although this procedure has not been accepted as the standard of care for patients with nephrosis, pharmacologic prophylaxis may already be practiced empirically, as in the present patient. We believe that our experience highlights the pitfalls of such a management in patients with nephrosis, implying the need for a diagnostic strategy for identifying those patients with NS who can benefit from prophylactic anticoagulation. Several concerns that emerged in this case are also discussed.

KEYWORDS: Retroperitoneal bleeding, nephrotic syndrome, prophylactic anticoagulation, heparin, minimal change disease

RECEIVED: April 12, 2017. **ACCEPTED:** July 3, 2017.

PEER REVIEW: Four peer reviewers contributed to the peer review report. Reviewers' reports totaled 645 words, excluding any confidential comments to the academic editor.

TYPE: Case Report

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported in part by a Grant-in-Aid for Research on Advanced Chronic Kidney Disease and Practical Research Project for Renal Diseases from the Japan Agency for Medical Research and Development, AMED.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Tetsu Akimoto, Division of Nephrology, Department of Internal Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-Shi 329-0498, Tochigi, Japan. Email: tetsu-a@jichi.ac.jp

Introduction

Patients with nephrotic syndrome (NS) have been shown to be at an increased risk of thromboembolic events.[1] The pathogenic basis for an association between NS and accelerated clotting activity is poorly understood; however, it is likely to depend on a net shift in the hemostatic balance toward a hypercoagulable state resulting from abnormal processing of prothrombotic and antithrombotic proteins.[2,3] Obviously, controlling the blood coagulation system with anticoagulant agents would be a useful therapeutic option for patients with nephrosis with overt thromboembolism,[1,4,5] and pharmacologic prophylaxis may be an attractive therapeutic option as well for asymptomatic patients who have NS, although the optimum anticoagulant strategy among overall subjects with the disease remains to be clarified.[1,4,5] We herein report our experience with a case of NS in a female patient who developed retroperitoneal bleeding during prophylactic anticoagulation with unfractionated heparin.

Case Report

A 75-year-old woman with a history of hypertension and hyperlipidemia, which had been treated by her general practitioner with rosuvastatin and doxazosin mesilate, complained of progressive swelling of her legs. Other significant findings were nausea, a loss of appetite, and easy fatigability appearing 6 weeks later, and she was therefore admitted to our teaching hospital when she was found to have NS with a reduced serum albumin (Alb) level of 1.8 g/dL and 4+ proteinuria despite having no apparent history of renal disease.

At the time of admission (clinical day 0), the patient had gained 8.6 kg in the previous 5 weeks, bringing her weight to 70.6 kg. She had neither dyspnea nor tachypnea, and no pains in the lower extremities were noted. Laboratory examinations revealed following the results: white blood cell count, 5600/μL; hemoglobin (Hb), 13.3 g/dL; platelet count, 190×10^3/μL; total protein, 4.2 g/dL; blood urea nitrogen, 16.0 mg/dL; serum creatinine (Cr), 1.3 mg/dL; fibrin/fibrinogen degradation products, 9.3 μg/mL; and D-dimer, 5600 μg/L. She was prescribed oral prednisolone (PSL) at a dose of 40 mg/day combined with intravenous furosemide and oral tolvaptan, and a renal biopsy was scheduled for 15 days later. While the patient was awaiting the procedure, intravenous pulse therapy with methyl-PSL (500 mg/day) was given for 3 consecutive days from clinical day 5 when her body weight increased to 74.5 kg. She was also started on intravenous unfractionated heparin with a titrated dosage ranging 10 000 from 12 500 U/day on the day of admission as prophylactic anticoagulation, which was planned to be continued at least until the day of the renal biopsy. Her active

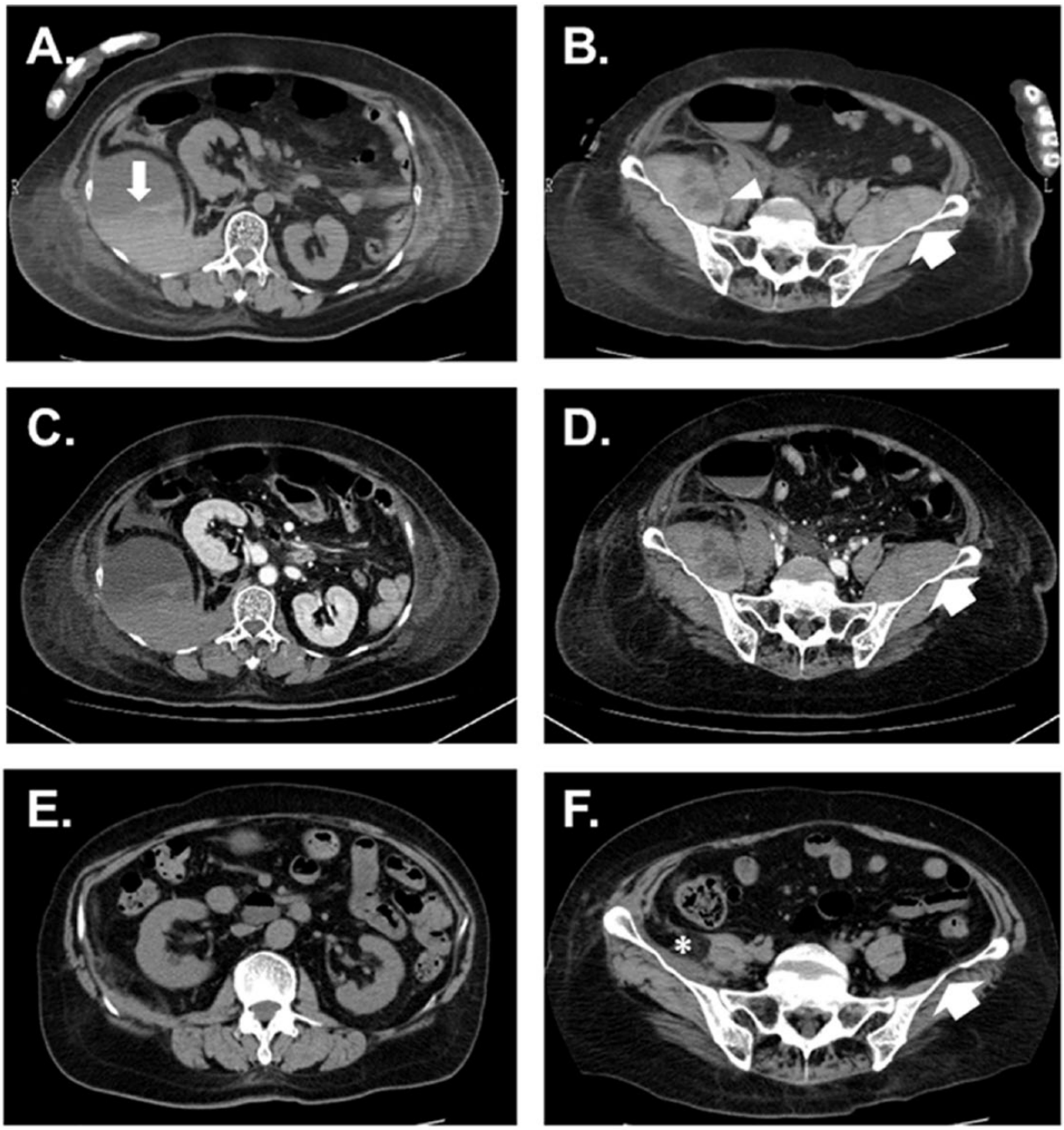

Figure 1. (A, C, and E) The findings of a diagnostic computed tomographic (CT) scan at L1 and (B, D, and F) the top of the sacrum. A noncontrast CT scan demonstrates a huge right-sided retroperitoneal collection with a hyperdense dependent layer (arrow in A), whereas the ipsilateral iliac muscle is shown to contain a fluid-fluid interface as well (arrowhead in B). (C and D) No seeping of the contrast material is demonstrated by a subsequent contrast-enhanced CT scan. (E and F) A distinct reduction in the size of the right iliac muscle (asterisk in F) as well as resolution of the right-sided hemorrhagic lesion was shown on repeat CT performed on clinical day 164. Note that there is a marked reduction in the size of the left iliac muscle as well (wide arrows in B, D, and F).

partial thromboplastin time (APTT) was sequentially monitored on a regular basis, ranging from 30.3 to 79.6 seconds, which corresponded to 1.3 to 2.9 times the control values. On clinical day 13, she started to complain of pain in the right back, groin, and thigh, which were gradually worsened in the next 2 days, and then, decreased blood pressure (BP) of 88/56 mm Hg suddenly developed when the urgent laboratory analysis revealed the declined Hb level of 8.3 g/dL. A diagnostic noncontrast abdominal computed tomographic (CT) scan demonstrated a huge right-sided retroperitoneal collection with extension to the ipsilateral pelvic iliac territory (Figure 1A and B). The clinical status of the patient steadily deteriorated thereafter despite vigorous management including cessation of intravenous heparin, volume resuscitation, transfusions of packed red blood cells, and the administration of vasopressors such as dopamine and norepinephrine for about 18 hours. She was therefore transferred to our hospital for further workup.

At the time of the transfer (clinical day 16), her consciousness level was E3V5M6 on the Glasgow Coma Scale with a decreased BP of 80/60 mm Hg, Hb level of 7.4 g/dL,

hematocrit of 22.2%, and a normal APTT of 26.6 seconds. Contrast-enhanced CT showed a massive retroperitoneal lesion without any seeping of the contrast material, whereas anteromedial displacement of the right kidney was demonstrated in the same manner as seen in the previous CT scan (Figure 1C and D). She underwent exploratory laparotomy, and after making the incision on the fascia of the right iliac muscle, a hematoma with partially liquefied blood clots was surgically evacuated, with no apparent bleeding site noted.

Her postoperative recovery was uneventful, and the pains in the right groin and thigh gradually disappeared with favorable improvements in her general status. We performed a renal biopsy 17 days after the transfer (clinical day 33), and her NS was thus ascribed to minimal change disease. At approximately 1 month after the renal biopsy (clinical day 61), she was still being treated with oral PSL (20 mg/d), having reached partial remission with a reduced amount of 24-hour urine protein of 0.6 g and an elevated serum Alb level of 3.4 g/dL while her serum Cr levels had settled around 0.6 mg/dL. Repeat abdominal CT performed on clinical day 164 showed the resolution of the retroperitoneal hemorrhagic lesion (Figure 1E and F).

Discussion

Retroperitoneal bleeding is a rare clinical entity with variable causes including percutaneous intervention, rupture of any kinds of vasculature, neoplasms, trauma, and cystic kidney or adrenal diseases.[6,7] It has also been shown in patients on systemic anticoagulation with warfarin, unfractionated heparin, or low-molecular-weight heparin.[7–9] Most anticoagulated patients do not have underlying structural abnormalities, whereas occult vasculopathy and/or arteriosclerosis, anticoagulant-mediated immune microangiopathy, and unrecognized minor trauma in the microcirculation may be involved in some subsets of patients with the disease.[7,10–12] In the current patient, a careful medical interview revealed that she had neither previous history of hemorrhagic complications nor prior experiences with anticoagulant medications for any of several pathologies such as atrial fibrillation, neoplasms, cerebrovascular diseases, orthopedic surgeries, and deep vein thrombosis. However, our patient had been in a supratherapeutic condition for a while during heparinization for prophylactic anticoagulation given the standard heparin dosing nomogram.[13] We feel this may have predisposed our patient, at least in part, to the disease, although we failed to precisely locate the bleeding point. However, numerous anticoagulated patients with therapeutic ranges of APTT or prothrombin time-international normalized ratio have also been shown to be complicated by retroperitoneal bleeding,[7–9,11,14] implying that the absence of excessive anticoagulation does not necessarily guarantee the feasibility and safety of such pharmacologic approaches.

Retroperitoneal bleeding in anticoagulated patients may clinically present as pain in the lower abdominal, flank, or inguinal area with radiation to the thigh and lumbar region. Hypotension and nerve-compression effects characterized by motor or sensory deficits in the groin and thigh may be additional suggestive signs.[7–9,11,15,16] A decline in the Hb level may also aid in a prompt diagnosis in this setting.[17] Although these manifestations should result in a high index of suspicion of the disease, we feel that an early diagnosis as well as awareness of the retroperitoneal bleeding remains a challenge for physicians, despite the accumulation of studies on the nature of the disease.[7–9,15,18,19] As in the present patient, simple regional pains without signs of neuropathy may instead be early presenting symptoms that can be easily overlooked, thereby resulting in diagnostic delay.[7,19]

The mainstay treatment for retroperitoneal bleeding includes withdrawal of the offending agents, correction of the anticoagulation state, volume resuscitation, and other supportive measures, and endovascular techniques and/or open surgical management can be additional therapeutic options.[7,11] Subjects with small hematomas and little to no neurological signs may respond well to conservative management, whereas more aggressive interventional approaches should be considered for patients with large hematomas, progressive neurological deficits, and/or hemodynamic instability.[7,11,16,20]

Although there is no clear consensus regarding the therapeutic decision, early detection and prompt treatment of the disease should result in a favorable outcome by reducing the time for hematoma development and subsequently lowering the duration of surrounding tissue compression.[19] In the present patient, we believe that a timely evacuation of the right side hematoma avoided the development of a prolonged or permanent disability resulting from the compression neuropathy. Alternatively, we may have underestimated the overall radiographic appearance of the pelvic region at the initial and second CT sessions and overlooked latent bleeding in the left iliac region. Indeed, it has been shown that a hematocrit effect, suggestive of the settling of blood elements,[10] is not necessarily associated with hemorrhagic events in the retroperitoneal territory.[21] Finally, we feel it is reasonable to consider that the distinct reduction in the size of the left iliac muscle confirmed on repeat CT might have reflected the spontaneous resolution of the disease, thereby encouraging us to speculate that our patient was complicated by bilateral retroperitoneal bleeding, which is regarded as a rare clinical entity.[14,15,19,20] Nevertheless, one may argue that the clinical evolution of the current patient is not surprising because the link between systemic heparinization and retroperitoneal bleeding has already been well described.[11,15,16] However, the significance of the present report should be evaluated carefully in terms of the controversy regarding prophylactic anticoagulation among patients with nephrosis.

We believe no one would argue against the primary role of the disease-related urinary losses of several coagulation regulatory proteins and a subsequent counterbalancing hemostatic protein synthesis in the establishment of a prothrombotic milieu among patients with NS,[1,2] although various aberrations of plasma procoagulant, anticoagulant, profibrinolytic,

Table 1. Aberrations of plasma procoagulant, anticoagulant, profibrinolytic, and antifibrinolytic proteins associated with nephrotic syndrome.

Factors II, VII, IX, X, and XI ↓
Factors V and VIII ↑
Antithrombin III ↓
Fibrinogen ↑
Plasminogen and tissue-type plasminogen activator ↓
Plasminogen activator inhibitor ↑

The plasma levels of each protein may increase (↑) or decrease (↓) with variable magnitude.

and antifibrinolytic proteins associated with NS have been demonstrated in previous studies (Table 1).[1–3] Given the controversy regarding pharmacologic prophylaxis for such a pathology among patients with nephrosis with glomerulopathies other than membranous nephropathy,[1–3] our management policy in the current case may invite criticism. However, the risk of venous thromboembolism may be significant even in patients with minimal change disease.[3] Indeed, several studies have described adult minimal change nephropathy complicated by pulmonary embolism.[22–24] Furthermore, adult patients with minimal change disease complicated by acute kidney injury, which are seen more frequently in older adults than in younger patients,[25] may have a severe hypercoagulable state.[24] The favorable decline in the serum Cr level along with a reduction in the urine protein level in the current patient implies the concurrent reversible acute kidney injury despite the lack of objective time course data indicating the functional status before the onset of NS. Finally, the low rate of reported adverse events with anticoagulation as well as our patient's markedly decreased serum Alb levels encouraged us to pursue heparinization prior to the renal biopsy as practiced empirically.[5,26] Because of the significant bleeding risk with the renal biopsy,[27] no one would argue against a periprocedural interruption of anticoagulation.[5,26] Although the clinical scenario of the present patient prevents an evaluation of the significance of the prophylaxis, our experience may highlight the pitfalls of such management, implying the need for a way to identify those patients with NS who can best benefit from the prophylactic anticoagulation. We believe that accumulating experiences from cases similar to ours will aid in establishing the indications and optimum regimen, including the appropriate timing, duration, preferred agent, and dosage, for prophylactic anticoagulation among patients with nephrosis, which remains an unresolved issue in the field of nephrology.

Author Contributions

MO and TA drafted the manuscript. MKa, TI, EH, MKo, AM, TMu, TS, and TMa made contributions to the acquisition of the clinical data. YO, YU, OS, SM, and DN provided a detailed review of the contents and structure of the manuscript, resulting in significant changes to the original document. All of the authors have read and approved the final manuscript.

Disclosures and Ethics

As a requirement for publication, the authors have provided the publisher with signed confirmation of their compliance with legal and ethical obligations including, but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) the protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this manuscript is unique and not under consideration for publication or published in any other journals and that they have permission from the rights holders to reproduce any copyrighted material. The external blind peer reviewers report no conflicts of interest.

REFERENCES

1. Pincus KJ, Hynicka LM. Prophylaxis of thromboembolic events in patients with nephrotic syndrome. *Ann Pharmacother*. 2013;47:725–734.
2. Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. *Thromb Res*. 2006;118:397–407.
3. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol*. 2012;7:513–520.
4. Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. *J Am Soc Nephrol*. 2007;18:2221–2225.
5. Akimoto T, Yamazaki T, Kusano E, Nagata D. Therapeutic dilemmas regarding anticoagulation: an experience in a patient with nephrotic syndrome, pulmonary embolism, and traumatic brain injury. *Clin Med Insights Case Rep*. 2016;9:103–107.
6. Igarashi Y, Akimoto T, Nukui A, et al. Flank pain, nausea, vomiting and hypotension in a chronic hemodialysis patient with a spontaneous perirenal hemorrhage. *Intern Med*. 2013;52:2083–2086.
7. Chan YC, Morales JP, Reidy JF, Taylor PR. Management of spontaneous and iatrogenic retroperitoneal haemorrhage: conservative management, endovascular intervention or open surgery? *Int J Clin Pract*. 2008;62:1604–1613.
8. González C, Penado S, Llata L, Valero C, Riancho JA. The clinical spectrum of retroperitoneal hematoma in anticoagulated patients. *Medicine (Baltimore)*. 2003;82:257–262.
9. Sunga KL, Bellolio MF, Gilmore RM, Cabrera D. Spontaneous retroperitoneal hematoma: etiology, characteristics, management, and outcome. *J Emerg Med*. 2012;43:e157–e161.
10. Torres GM, Cernigliaro JG, Abbitt PL, et al. Iliopsoas compartment: normal anatomy and pathologic processes. *Radiographics*. 1995;15:1285–1297.
11. Park SH, Lee SW, Jeon U, et al. Transcatheter arterial embolization as treatment for a life-threatening retroperitoneal hemorrhage complicating heparin therapy. *Korean J Intern Med*. 2011;26:352–355.
12. McCort JJ. Intraperitoneal and retroperitoneal hemorrhage. *Radiol Clin North Am*. 1976;14:391–405.
13. Garcia DA, Baglin TP, Weitz JI, Samama MM; American College of Chest Physicians. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e24S-e43S.
14. Wada Y, Yanagihara C, Nishimura Y. Bilateral iliopsoas hematomas complicating anticoagulant therapy. *Intern Med*. 2005;44:641–643.
15. Niakan E, Carbone JE, Adams M, Schroeder FM. Anticoagulants, iliopsoas hematoma and femoral nerve compression. *Am Fam Physician*. 1991;44:2100–2102.

16. Parmer SS, Carpenter JP, Fairman RM, Velazquez OC, Mitchell ME. Femoral neuropathy following retroperitoneal hemorrhage: case series and review of the literature. *Ann Vasc Surg*. 2006;20:536–540.
17. Ernits M, Mohan PS, Fares LG II, Hardy H III. A retroperitoneal bleed induced by enoxaparin therapy. *Am Surg*. 2005;71:430–433.
18. Merrick HW, Zeiss J, Woldenberg LS. Percutaneous decompression for femoral neuropathy secondary to heparin-induced retroperitoneal hematoma: case report and review of the literature. *Am Surg*. 1991;57:706–711.
19. Sasson Z, Mangat I, Peckham KA. Spontaneous iliopsoas hematoma in patients with unstable coronary syndromes receiving intravenous heparin in therapeutic doses. *Can J Cardiol*. 1996;12:490–494.
20. Basheer A, Jain R, Anton T, Rock J. Bilateral iliopsoas hematoma: case report and literature review. *Surg Neurol Int*. 2013;4:121.
21. Lenchik L, Dovgan DJ, Kier R. CT of the iliopsoas compartment: value in differentiating tumor, abscess, and hematoma. *AJR Am J Roentgenol*. 1994;162:83–86.
22. Matsuda A, Tsuchiya K, Yabuki Y, et al. Fatal diffuse pulmonary arterial thrombosis as a complication of nephrotic syndrome. *Clin Exp Nephrol*. 2007;11:316–320.
23. Chen SC, Liu WC, Lee CH, Chang JM, Chen HC. Nephrotic syndrome complicated by life-threatening pulmonary embolism in an adult patient. *Kaohsiung J Med Sci*. 2010;26:89–95.
24. Huang MJ, Wei RB, Su TY, et al. Impact of acute kidney injury on coagulation in adult minimal change nephropathy. *Medicine (Baltimore)*. 2016;95:e5366.
25. Waldman M, Crew RJ, Valeri A, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol*. 2007;2:445–453.
26. Medjeral-Thomas N, Ziaj S, Condon M, et al. Retrospective analysis of a novel regimen for the prevention of venous thromboembolism in nephrotic syndrome. *Clin J Am Soc Nephrol*. 2014;9:478–483.
27. Cook BW. Anticoagulation management. *Semin Intervent Radiol*. 2010;27:360–367.