Clin Exp Nephrol (2016) 20:212–217
DOI 10.1007/s10157-015-1149-4

ORIGINAL ARTICLE

Risk factors of venous thromboembolism in focal segmental glomerulosclerosis with nephrotic syndrome

Shi-jun Li[1] · Yuan-Mao Tu[1] · Chang-sheng Zhou[2] · Li-Hua Zhang[1] · Zhi-hong Liu[1]

Received: 21 May 2015 / Accepted: 21 July 2015 / Published online: 29 July 2015

Abstract
Background Venous thromboembolism (VTE) is an important and potentially life-threatening complication in focal segmental glomerulosclerosis (FSGS). The aim of this study was to investigate the prevalence and predisposing risk factors of venous thromboembolism in patients with FSGS with nephrotic syndrome.
Methods A total of 120 FSGS patients with nephrotic syndrome were enrolled in this study. Venous thromboembolism was confirmed by contrast-enhanced dual-source computed tomography angiography or magnetic resonance venography. Potential clinical and laboratory risk factors for VTE were screened.
Results Venous thrombosis was demonstrated in 12 (10 %) patients. Venous thrombosis occurred during the first episode of nephrotic syndrome in 3 patients and during a relapse in 9 patients. Eight patients had a pulmonary embolism, four had a renal vein thrombosis, three had a lower limb deep vein thrombosis, one had a cerebral sinovenous thrombosis, and one had a portal vein thrombosis. The positive predictive value for the D-dimer level was 22.4 % in the patients with FSGS, and the negative predictive value for the D-dimer level was 100 %. Of the screened risk factors, higher hematocrit and relapse of nephrotic syndrome were risk factors for VTE. Other risk factors, such as proteinuria, hypoalbuminemia, platelet count, fibrinogen level, and antithrombin III level, were not risk factors for VTE in patients with FSGS.
Conclusion We found that the prevalence of venous thromboembolism is approximately 10 % in FSGS patients with nephrotic syndrome. Most of the patients had a PE. Hemoconcentration and relapse of nephrotic syndrome were risk factors for the development of VTE in FSGS. Negative D-dimer may exclude venous thromboembolism in patients with nephrotic syndrome.

Keywords Focal segmental glomerulosclerosis · Venous thromboembolism · Computed tomography angiography

Introduction

Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of idiopathic nephrotic syndrome. The incidence of FSGS has increased in the past decade [1]. Some patients with FSGS are steroid-resistant or steroid-dependent and frequently relapse (FR), which induces persistent nephrotic range proteinuria and hypoalbuminemia [2, 3]. Persistent hypoalbuminemia is associated with a hypercoagulable state and an increased risk of venous thromboembolism (VTE), the consequence of which is potentially life-threatening, [4, 5]. However, the incidence of VTE in patients with FSGS has been reported based on only a few retrospective studies [6]. The absolute risk of VTE in patients with FSGS with nephrotic syndrome remains uncertain. Therefore, risk factors of VTE need to be further investigated using a cohort of FSGS patients. This single-center cross-sectional study was performed to evaluate the prevalence of VTE and identify risk

✉ Shi-jun Li
lisj8855@163.com

[1] National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, People's Republic of China

[2] Department of Medical Imaging, Jinling Hospital, Nanjing University School of Medicine, Nanjing, People's Republic of China

factors for thromboembolic events in biopsy-proven FSGS patients.

Patients and methods

Patients

This was a cross-sectional study. The inclusion criteria for patient enrollment were as follows: (1) The histologic and immunopathologic changes were consistent with FSGS; (2) 24-h urine protein excretion was greater than 3.5 g, serum albumin level less than 30 g/L. The exclusion criteria included: (1) Secondary forms of FSGS, such as: obesity, systemic hypertension, human immunodeficiency virus-associated disease; (2) exposure to classic risk factors for venous thrombosis such as antiphospholipid syndrome, cancer, major surgery, prolonged immobilization; and (3) use of oral contraceptives or prophylactic anticoagulation prior to the time of inclusion.

From January 2012 to January 2014, 258 consecutive in-hospital FSGS patients were initially screened in our center, and 175 patients fit the inclusion criteria. Forty patients were further excluded. Eighteen of whom had a secondary form of disease, and 22 were on prophylactic anticoagulation treatment. Thus, a total of 135 patients were recruited into this study. However, 15 patients refused to receive CT angiography. The remaining 120 patients completed the study (Fig. 1). This study was approved by the Ethical Committee of our hospital (number: JL-2011/245). According to the ethics committee recommendations, written consent, including a detailed description of the CT angiography procedure, was obtained from all patients before CT angiography. Consent was recorded in the medical chart of each patient. Patients had the opportunity to decline participation in the study at any time.

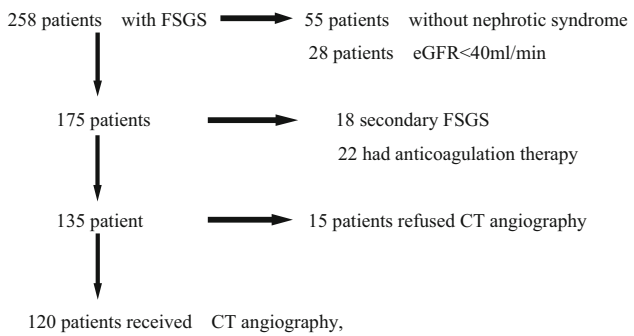

Fig. 1 Flowchart for inclusion in patients with FSGS

Data collection

Baseline information at the time of CT angiography was collected from all patients, including sex, age, duration of renal diseases, hypertension, and ultrasonography of bilateral kidneys. A detailed medical history was recorded to document any past or present history of thrombosis episodes in the form of flank pain, macroscopic hematuria, hemoptysis, dyspnea and pleuritic pain.

Laboratory measurements

Laboratory measurements included a routine urinalysis, which included 24-h urine protein, plasma urea, serum creatinine, albumin, lipids and blood sugar. Coagulation detection was composed of (1) hemoglobin, hematocrit, platelet count, (2) plasma fibrinogen, (3) prothrombin time (PT), (4) activated partial thromboplastin time (APTT), (5) serum antithrombin III levels (radioimmunodiffusion assay; normal range (28.42 ± 2.07) mg/dL; AT-III <25 mg/dL was defined as AT-III deficiency), and (6) plasma D-dimer level (enzyme-linked immunoabsorbent assay [ELISA]; D-dimer >0.5 mg/dL was defined as positive).

Imaging

Computed tomography pulmonary angiography (CTPA) and CT venography (CTV) were performed in 120 patients. Seventy of the patients were at the onset of nephrotic syndrome, and 50 patients were tested during a relapse nephrotic syndrome. CT examinations were performed on a dual-source CT scanner (Somatom Definition; Siemens Medical Solutions). Lower limb DVT was detected by compression venous ultrasonography in all included patients. Magnetic resonance venography (MRV) was performed only if the patients had clinical presentations of cerebral venous thrombosis.

Renal vein thrombosis was diagnosed once either complete or partial filling defects within the renal vein were present. For CTPA, continuous filling defects that extended into branching vessels were considered as a single PE at the most proximal location. For lung blood flow imaging (BFI), lobar or segmental wedge-shaped perfusion defects were considered positive for PE [7]. Cerebral venous thrombosis was diagnosed by magnetic resonance venography (MRV). Thrombi diagnosed simultaneously at different sites were considered a single event. Images were reviewed independently by two experienced radiologists, and they achieved a consensus diagnosis. Lower limb DVT was diagnosed by compression venous ultrasonography.

Statistical analysis

Statistical analyses were performed using SPSS software, version 15.0 (SPSS Inc. Chicago, IL, USA). Quantitative variables were expressed as the mean ± SD or the medians (ranges) for data with an abnormal distribution. Categorical variables were expressed as a frequency or percentage. Comparisons between two groups were tested using Student's t test, Mann–Whitney U test for data with abnormal distribution or a X^2 test for categorical data. The potential risk factors for VTE were evaluated in the entire cohort using a univariate logistic regression analysis. P values less than 0.05 were regarded as significant.

Results

Imaging findings

Of the 120 patients (89 males and 31 females, age range 12–69 years) with FSGS, 12 patients (10 %) had VTE. A total of 21 anatomic site VTEs were detected in these patients, and 8 patients had simultaneous VTEs at more than one site. Eight patients (6.67 %) had a PE; 4 (3.33 %) had an RVT; 3 had a popliteal vein thrombosis; 1 had a portal vein thrombosis (extends to splenic vein and superior mesenteric vein) (Fig. 2a); 1 had a cerebral sinovenous thrombosis (CSVT) (Fig. 2b); and 1 had a superior vena cava thrombosis and inferior vena cava thrombosis (Table 1).

Using CTPA and lung blood flow imaging, 8 patients had a PE (Fig. 2c, d). Four of these patients had simultaneous RVT and PE; one had a superior vena cava thrombosis and PE; one had popliteal vein thrombosis and PE; and the remaining two had only a PE. Dyspnea or chest pain was present in the 5 patients with a PE. Three of these patients also had hypoxemia. None of these patients presented with hypotension. A PE localized in the lobar pulmonary artery embolism was confirmed by CTPA in the 5 symptomatic patients. The remaining 3 patients with segmental pulmonary artery embolism had no clinical signs of PE by lung blood flow imaging.

Four patients had an RVT, 2 had a left RVT, and 2 had a right RVT. All the RVT patients also had a PE. An RVT extended beyond the renal vein to the inferior vena cava in 1 patient. The characteristic clinical symptoms of flank pain were not present in the patients with an RVT. Gross hematuria and acute renal injury were also not found in these patients. A CTV scan revealed a thrombosis in the trunk of the portal vein extending to the superior mesenteric vein and splenic vein in one patient with abdominal distention and a great quantity of ascites. A popliteal vein thrombosis was confirmed by compression ultrasound in 3 patients (2 in the left, 1 in the right). All three patients had a swollen lower leg that was larger than the unaffected leg. One patient presented with a severe headache, vomiting and blurred vision, cerebral magnetic resonance venography (MRV) showed a thrombosis of the transverse and sigmoid sinus.

The clinical characteristics of patients at the time when CT angiographies were performed are shown in Table 2. The patients with thrombosis were younger than those without thrombosis, but the difference was not significant. VTE was found at the first episode of nephrotic syndrome in 3 patients (4.28 %, 3/70) and at the time of nephrotic syndrome relapse in 9 patients (18.0 %, 9/50). No significant difference was found in serum albumin, 24-h protein excretion, serum creatinine or cholesterol between the patients with and without thrombosis.

Coagulation findings

Plasma D-dimer was positive in 12 (100 %) patients with thrombosis. Plasma D-dimer was positive in 38 (35.2 %) patients without VTE. The positive rate of D-dimer was significantly higher in the patients with a thrombus than in those without a thrombus ($P < 0.01$). The sensitivity and specificity of D-dimer were 100 and 64.8 %, respectively, in the patients with VTE. The positive predictive value (PPV) and the negative predictive value (NPV) for the D-dimer level were 24 and 100 %, respectively, in the patients with VTE. The hematocrit level was higher than 50 % in 6 patients and higher than 60 % in 2 patients. Two patients had diarrhea before a thrombosis event, and the remaining 4 patients had a history of diuretic use. The hemoglobin and hematocrit level was significantly higher in the patients with thrombosis compared with those without thrombosis ($P = 0.01$) (Table 2). Decreased AT III levels were noted in 83 % of patients with thrombosis and 86.9 % of patients without thrombosis. There was no difference in fibrinogen levels or the platelet count between the patients with and without thrombosis in FSGS.

Analysis of risk factors

The results of the univariable analyses to identify clinical features associated with the development of VTE are shown in Table 3. Higher hemoglobin and hematocrit and relapse of nephrotic syndrome were risk factors for the development of VTE in patients with FSGS (Table 3). Other clinical features, such as proteinuria, hypoalbuminemia, platelet count, fibrinogen levels, and AT III levels, did not reach statistical significance as risk factors for VTE in the patients with FSGS.

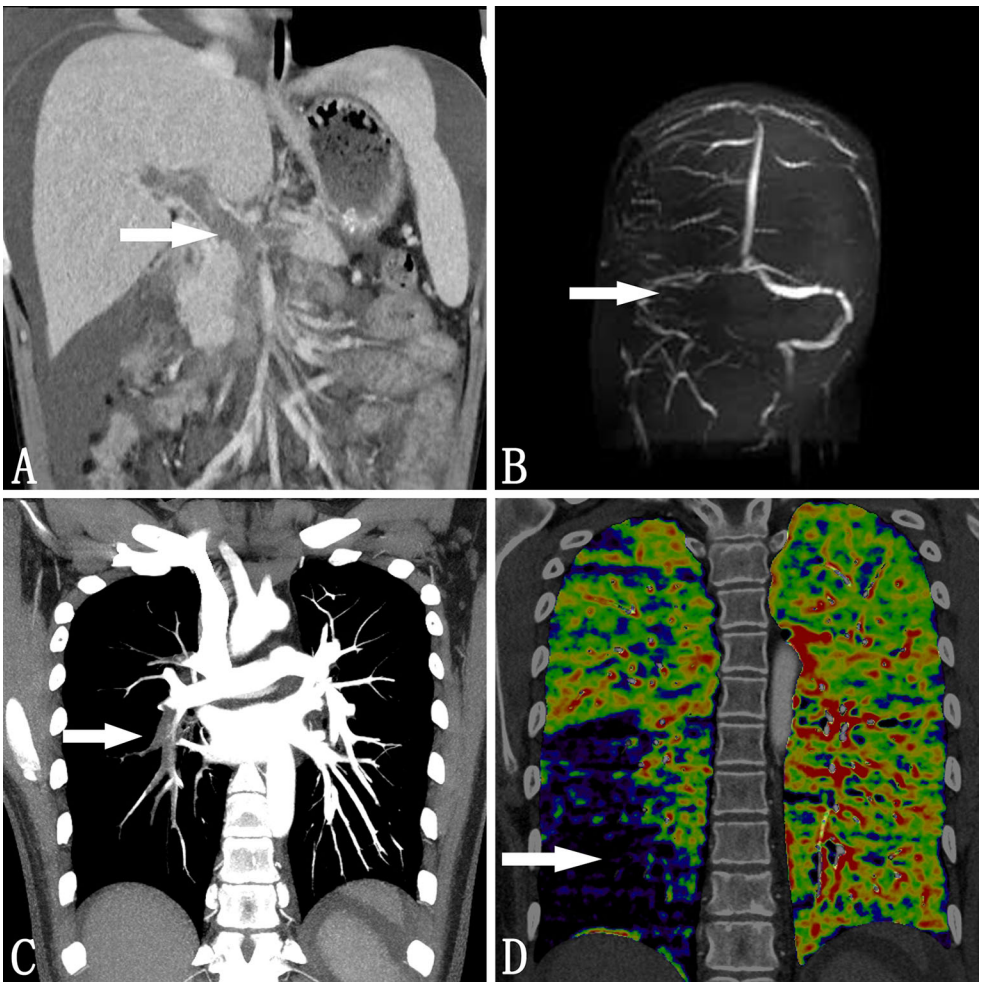

Fig. 2 Localization of VTE and PE in FSGS patient. **a** CT venography image shows the filling defect in the trunk of the portal vein (*arrow*) case 2. **b** Contrast-enhanced MR venography image shows the filling defect in the right sigmoid sinus (*arrow*) case 9. **c** Coronal reformatted CT pulmonary angiography image showed right inferior pulmonary artery embolism (*arrow*) case 12. **d** Blood flow images derived from dual energy contrast-enhanced CT pulmonary angiography show the perfusion defects in the right lower lung lobe (*arrows*) case 12

Discussion

In the present study, we found that the prevalence of VTE was 10 % in 120 patients with FSGS. We identified VTEs at different sites, including a PE, DVT of the lower extremities, RVT, and other sites of venous, such as a portal vein thrombosis and cerebral sinovenous thrombosis (CVT). However, portal vein thrombosis has a relatively low incidence in patients with nephrotic syndrome [8]. Most sinovenous thrombosis as a complication with nephrotic syndrome is reported in children [9]. The characteristic symptom of CVT is persistent headache. The characteristic symptom of portal vein thrombosis is abdominal distention and a large quantity of ascites. Therefore, we suggest that clinicians should keep in mind that a VTE may occur at any venous site in FSGS patients. CTV or MRV is recommended for patients suspected with symptom of VTE.

D-dimer is a degradation product of cross-linked fibrin. D-dimer levels are elevated in plasma in the presence of an acute clot because of the simultaneous activation of coagulation and fibrinolysis. Hence, a normal D-dimer level makes a PE unlikely [10]. However, to our knowledge, it is unknown whether D-dimer screening is relievable for exclusion of VTE in nephrotic patients. In this study, the negative predictive value (NPV) of D-dimer is 100 %, and the positive predictive value (PPV) of D-dimer is 24 % in patients with FSGS. Therefore, D-dimer is a useful test for ruling out VTE and should be routinely measured in nephrotic patients. A negative D-dimer may exclude VTE in patients with NS. CT venography or an MRV assessment is not considered an essential part of the evaluation in nephrotic patients who are D-dimer negative.

The disease-specific risk of VTE in patients with nephrotic syndrome remains an area of significant uncertainty. In a retrospective study [11], there was no observed

Table 1 Clinical features of patients with venous thrombosis in FSGS

Patient	Sex	Age (year)	Course of disease (m)	Hb (g/L)	Hematocrit (%)	Albumin (g/L)	Proteinuria (g/24 h)	D-Dimer (mg/dL)	Clinical symptoms of thrombosis	Site of thrombosis
1	M	41	1	188	56	18.7	11.0	1.5	Dyspnea	PE + RVT
2	M	19	18	198	58	22.2	10.3	0.5	Abdominal distention	Portal vein
3	M	22	24	146	43	21.6	5.67	0.8	Right leg swollen	PVT
4	M	23	12	165	51	15.2	5.78	1.1	Left leg swollen	PVT
5	F	69	14	121	35	24.8	4.26	2.5	Right leg swollen	PE + PVT
6	F	15	6	204	61	18.4	11.8	1.3	Dyspnea	PE + RVT
7	M	17	10	221	65	22.5	9.97	1.9	Chest pain	PE + RVT
8	M	66	0.8	121	34	23.1	7.14	2.7	No	PE + SUVCT
9	F	39	13	147	44	19.0	13.7	1.0	Headache vomiting	CSVT
10	M	16	0.9	162	50	18.4	4.37	0.4	Dyspnea	PE
11	M	20	84	116	34	14.3	5.46	1.2	No	PE
12	M	16	11	190	57	16.6	6.24	2.4	Dyspnea	PE + RVT +IVCT

PE pulmonary embolism; *RVT* renal vein thrombosis, *CSVT* cerebral sinovenous thrombosis, *PVT* popliteal vein thrombosis. *SUVCT* superior vena cava thrombosis, *IVCT* inferior vena cava thrombosis

Table 2 Laboratory findings of FSGS with or without thrombosis

	Thrombus group ($n = 12$)	No thrombus group ($n = 108$)	*P*
Age (year)	30.3 ± 19.4	33.5 ± 16.4	0.29
Male, *n* (%)	9 (75)	80 (74.1)	1.00
Proteinuria (g/24 h)	7.97 ± 3.20	8.05 ± 4.15	0.95
Serum albumin (g/L)	19.5 ± 3.28	20.6 ± 4.15	0.42
Serum creatinine (μmol/L)	116 ± 47.7	130 ± 58.3	0.19
Total cholesterol (mmol/L)	10.9 ± 3.48	10.8 ± 4.24	0.94
Hematuria, *n* (%)	4 (33.3)	54 (50.0)	0.20
Hemoglobin (g/L)	165 ± 35.5	136 ± 23.3	0.01
Hematocrit (%)	49 ± 11	41 ± 08	0.01
Blood platelet count (10^9/L)	25.1 ± 6.81	25.4 ± 8.70	0.87
Prothrombin time (s)	11.0 ± 0.72	10.8 ± 1.67	0.44
Fibrinogen (mg/L)	446 ± 173	463 ± 103	0.77
D-dimer positive, *n* (%)	12 (100)	38 (35.1)	<0.01
Antithrombin III (mg/dL)	17.2 ± 6.51	18.8 ± 5.81	0.47

difference in the incidence of VTE between MN and FSGS. However, other studies have shown that patients with MN have a greater risk of VTE (7.9 %) compared with those with FSGS (3.4 %) or IgAN (0.4 %) [12]. In our previous study, the incidence of thromboembolism was 36 % in MN patients [13]. Interestingly, MN was associated with a particularly high risk of RVT. Most of these RVTs were asymptomatic [13]. However, there were fewer asymptomatic RVTs in the FSGS patients by routine CTV screening in this study. Therefore, further research is required to identify reasons for the disease-specific risk of VTEs in patients with NS.

The pathophysiology of thrombogenesis in nephrotic syndrome is not completely understood, but it seems to be multifactorial. Proteinuria is recognized to be correlated with an increased risk of thrombosis development [14]. Mahmoodi et al. [11] showed that proteinuria and serum albumin levels tended to be related to VTE. Another study demonstrated that, compared with those who did not have proteinuria, patients who tested positive for proteinuria had a 3.4-fold increased risk of VTE [15]. However, in this study, proteinuria and serum albumin were not risk factors for the development of VTE in FSGS. Endogenous anticoagulant AT III deficiency has been suggested as a possible cause of thromboembolic complications [16]. Our results also revealed that antithrombin III deficiency was common (>80 %) in FSGS patients but not related to VTE events. Interestingly, most of the VTEs occurred at a relapse of severe nephrotic syndrome. The hematocrit level of patients with a thrombus was higher than that in patients

Table 3 Univariable analyses: risk factors of venous thromboembolism

Risk factors	Odd ratios	95.0 % CI	*P* value
Relapse of NS	4.9	1.25–19.2	<0.05
Male	0.95	0.24–3.77	0.94
D-dimer (mg/dL)	7.47	2.62–21.3	<0.01
ATIII (mg/dL)	0.95	0.82–1.09	0.46
Fibrinogen (mg/L)	0.99	0.99–1.00	0.63
Proteinuria (g/24 h)	0.99	0.86–1.16	0.95
Serum albumin (g/L)	0.93	0.79–1.10	0.41
Hemoglobin (g/L)	1.63	1.23–2.15	<0.01
Hematocrit (%)	1.15	1.06–1.26	<0.01
Blood platelet count (10^9/L)	0.99	0.93–1.07	0.88

without a thrombus. Taken together, the pathogenesis of VTE in patients with FSGS may be multifactorial. Therefore, it would be reasonable to hypothesize that hemoconcentration may contribute to FSGS thromboembolic development.

This study has important clinical implications for FSGS. First, to the best of our knowledge, this was the largest cross-sectional study on the prevalence of VTE in patients with FSGS. Second, this study is noteworthy because we found that VTE event may be related to hemoconcentration in nephrotic syndrome, and most of the VTEs occurred during a relapse of nephrotic syndrome. Third, we found that D-dimer is a useful test for ruling out a VTE, and a negative D-dimer may exclude VTEs in patients with NS.

There were some limitations in this study. First, the rate of VTE might be underestimated in this cross-sectional study because the patients may subsequently develop VTE at the next relapse. This may have biased our results toward diagnosing fewer VTE in the patients with FSGS. Second, despite the relatively large size of our cohort, there were relatively few VTE events; multivariate study cannot be done theoretically in this study to identify independent risk factor.

In summary, we found that the prevalence of venous thromboembolism is approximately 10 % in FSGS patients with nephrotic syndrome. Most of the patients had a PE. Hemoconcentration and relapse of NS were risk factors for the development of VTE in FSGS. Negative D-dimer may exclude venous thromboembolism in patients with nephrotic syndrome.

Acknowledgments The authors acknowledge support from the National Natural Science Foundation of China (No. 81270799).

Compliance with ethical standards

Conflict of interest The authors declare that they have no other relevant financial interests.

References

1. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int. 2004;66:920–3.
2. D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365:2398–411.
3. Korbet SM. Treatment of primary FSGS in adults. J Am Soc Nephrol. 2012;23:1769–76.
4. Loscalzo J. Venous thrombosis in the nephrotic syndrome. N Engl J Med. 2013;368:956–8.
5. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome–associated thromboembolic disease. Clin J Am Soc Nephrol. 2012;7:513–20.
6. Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. Thromb Res. 2006;118:397–407.
7. Zhang LJ, Zhao YE, Wu SY, Yeh BM, Zhou CS, Hu XB, Hu QJ, Lu GM. Pulmonary embolism detection with dual-energy CT: experimental study of dual-source CT in rabbits. Radiology. 2009;252:61–70.
8. Etoh Y, Ohsawa I, Fujita T, Fuke Y, Endo M, Ohi H, Kumasaka K. Nephrotic syndrome with portal, splenic and renal vein thrombosis. Nephron. 2002;92:680–4.
9. Suri D, Ahluwalia J, Saxena AK, et al. Thromboembolic complications in childhood nephrotic syndrome: a clinical profile. Clin Exp Nephrol. 2014;18:803–13.
10. Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, Biel RK, Bharadia V, Kalra NK. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med. 2004;140:589–602.
11. Mahmoodi BK, ten Kate MK, Waanders F, Veeger NJ, Brouwer JL, Vogt L, Navis G, van der Meer J. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. Circulation. 2008;117:224–30.
12. Barbour SJ, Greenwald A, Djurdjev O, Levin A, Hladunewich MA, Nachman PH, Hogan SL, Cattran DC, Reich HN. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. Kidney Int. 2012;81:190–5.
13. Li SJ, Guo JZ, Zuo K, Zhang J, Wu Y, Zhou CS, Lu GM, Liu ZH. Thromboembolic complications in membranous nephropathy patients with nephrotic syndrome—a prospective study. Thromb Res. 2012;130:501–5.
14. Barbano B, Gigante A, Amoroso A, Cianci R. Thrombosis in nephrotic syndrome. Semin Thromb Hemost. 2013;39:469–76.
15. Kato S, Chernyavsky S, Tokita JE, Shimada YJ, Homel P, Rosen H, Winchester JF. Relationship between proteinuria and venous thromboembolism. J Thromb Thrombolysis. 2010;30:281–5.
16. Kauffmann RH, Velgkamp JJ, Van Tilburg NH, Van Es LA. Acuqired antithrombin III deficiency and thrombosis in the nephrotic syndrome. Am J Med. 1978;65:607–13.