Case Report

Renal vein thrombosis and membranous glomerulopathy in a patient homozygote for factor V Leiden mutation: A mere coincidence?

Membranous nephropathy, the most common primary cause of nephrotic syndrome in adults, is associated with development of renal vein thrombosis. The cause and effect relationship between the two entities has been controversial for years, but currently the accepted concept is that nephrotic syndrome induces a hypercoagulable state through a urinary loss of anti-coagulative proteins, such as antithrombin III. This, in turn, leads to venous thrombosis, most commonly within the renal vein (since anticoagulant factors are especially depleted in post-glomerular efflux) (1) . The opposed hypothesis states that hypercoagulable state may cause renal vein thrombosis, which initiates membranous glomerulopathy through disruption of renal blood drainage, but it has been generally abandoned in recent years, in the perspective of ample data indicating the central role of immune-mediated glomerular damage in this disorder. However, rejection of this theory was predominantly based on studies performed prior to the currently expanding recognition of many common inherited hypercoagulative disorders.

Described herein is a patient homozygous to factor V Leiden mutation who presented with pulmonary thromboembolism and later developed renal vein thrombosis and membranous nephropathy. Anticoagulant treatment was associated with prompt resolution of renal vein thrombosis that was followed by a delayed but gradual improvement of proteinuria. This report raises the question of the possibility of an association between activated protein C resistance, renal vein thrombosis, and membranous glomerulopathy. The coexistence of factor V Leiden mutation and membranous glomerulopathy may serve as predisposing risk factors to the development of renal vein thrombosis. Alternatively, in a minority of cases hypercoagulative states and renal vein thrombosis might precede and initiate secondary renal glomerulopathy. Until future studies establish whether a linkage exists between hypercoagulable disorders and membranous nephropathy, we suggest that a full hypercoagulability work-up be performed in those patients with the nephritic syndrome secondary to membranous glomerulopathy who develop renal vein thrombosis.

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Case report

A 43-year-old previously healthy male dentist was admitted to another hospital because of right-sided pleuritic chest pain, hemoptysis and shortness of breath. Physical examination was reportedly unremarkable. Blood count, renal function tests, hepatic aminotransferase, albumin and cholesterol levels were all within normal levels and urinalysis was normal. Chest radiography revealed right-sided segmental atelectasis, yet bronchoscopy was reported to be unremarkable. Echocardiography and abdominal ultrasonography were normal. The patient was erroneously diagnosed of suffering from pleuridinia, was administered analgesics (Naproxen, 250 mg bid) and discharged.

In the following five months, the patient continued to suffer from repeated episodes of chest pain and hemoptysis, and progressively developed dyspnea on exertion. He denied any personal or familial history of thrombophillia, cardiac disease, and the use of medications, natural remedies, recreational drugs, alcohol, or potential exposure to human immunodeficiency virus.

On admission the patient was afebrile and mildly dyspneic. Blood pressure was 150/95, heart rate was 115, and respiratory rate was 15 per minute, with peripheral oxygen saturation 93% on room air. Periorbital swelling and mild symmetric pedal edemas were noted, without physical signs of deep vein thrombosis. The physical examination was otherwise unremarkable. Laboratory tests on admission are presented in Table 1. Of note is the severe hypoalbuminemia of 24 g/l and hypercholesterolemia, with a total serum cholesterol level of 7 mM and LDL level of 5 mM. Urinalysis showed hyaline casts. Nephrotic range proteinuria of 6.4 g/day was noted. Chest radiography and echocardiography were normal. Computerized tomography of the chest and abdomen revealed a small, peripheral right-sided pulmonary embolus, and a large thrombus within the vena cava originating at the level of the right renal vein and extending cranially beyond the hepatic veins (Fig. 1). The venous system caudal to the renal veins was patent. The deep venous system in the lower limbs appeared normal on ultrasound and Doppler studies.

Thrombophillia survey revealed the diagnosis of homozygosis for factor V Leiden mutation-associated activated protein C resistance (APCR). Evaluation of secondary causes of nephrotic syndrome was negative, including tests for anti-nuclear and anti cardiolipin antibodies, C & P ANCA, anti nRNP, rheumatoid factor, and cryoglobulins. Serology for hepatitis B and C viruses, Human Immunodeficiency virus and syphilis were all negative. Protein- and immunoelectrophoresis, as well as tumor markers were normal, rectal biopsy was negative for amyloid, and urinary heavy metals were not increased.

The patient was treated with warfarin (for an INR of 2–3), enalapril and simvastatin. The respiratory symptoms and microscopic hematuria quickly resolved. Repeated imaging after a month confirmed patency of the vena cava and a normal renal

venous flow. Six months after the initiation of anticoagulant therapy nephrotic-range proteinuria persisted and the patient underwent right kidney biopsy that was significant for mild glomerular thickening, mesangial cell proliferation, mononuclear infiltrate and foci of fibrosis. Renal tubuli and blood vessels appeared normal. Fluorescence microscopy showed diffuse granular deposits, mainly consisting of IgG and IgM, some focal C3 deposits along glomeruli and small blood vessels, compatible with membranous glomerulopathy. Electron microscopy revealed sub-epithelial deposits, characteristic of membranous glomerulopathy (Fig. 2). Congo-Red staining was negative for amyloidosis. The patient declined immunosuppressive regimens. During 5 years of follow-up he remained asymptomatic, with normal blood pressure and kidney function tests. Proteinuria, which reached a high of over 6 grams per day at the peak of disease activity (Fig. 3), gradually reduced to 400 mg per day after a year and a half of follow-up, and remained stable throughout the 5 years of follow-up.

Discussion

We report a patient who presented with prolonged clinical signs of recurrent pulmonary emboli and was later found to have a vena cava thrombus, originating from the right renal vein. Further evaluation revealed the presence of both membranous glomerulonephritis and homozygosity for factor V Leiden mutation, associated with APCR. To our knowledge, the association between this and other inherited thrombophilias, RVT and membranous nephropathy has not been suggested previously.

The gene incidence of factor V Leiden mutation is about 3–6.7% in the general population. Thus, homogzygocity for the mutation ranges from 1/1,000 to 4/10,000 (2–4). The incidence of membranous glomerulonephritis is estimated to be 2/100,000 per year (for young age group), which make the probability of concurrently developing both disorders extremely low, a chance of 0.8–2/100,000,000 per year. The very low probability of the patient coincidently having both diseases, as well as the spontaneous long-lasting remission, without relapses of membranous glomerulopathy (over a five year period of follow-up) raises the possibility of a pathophysiological linkage. However, true epidemiological validation of such linkage can only be achieved if future studies demonstrate an increased incidence of membranous glomerulopathy in patients with homozygous factor V Leiden mutation. Alternatively, a possibility exists that an undiagnosed hypercoagulability disorder in a patient suffering from membranous nephropathy may predispose him to the development of renal vein thrombosis.

Membranous nephropathy, the most common primary cause of nephrotic syndrome in adults, is closely associated with the development of RVT, which has been reported in up to 10% of cases (5–8). The cause and effect relationship between the two disease entities has for years been the subject of major debate (9), but currently the general opinion is that nephrotic syndrome predisposes to hypercoagulability and particularly to RVT. A hypercoagulable state in nephrotic patients is secondary to increased platelet activation and the generation of high molecular weight fibrinogen molecules. It is conceivable that urinary loss of anticoagulate proteins such as anti-thrombin III leads to the particular thrombophyllic tendency in the renal efflux (10, 11). Others

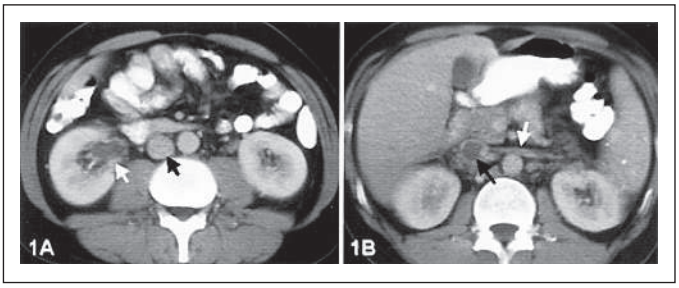

Figure 1: A) Axial CT at the level of the right renal vein demonstrating thrombosis of the vein (white arrow). The IVC at this level is patent (black arrow). B) Axial CT slightly cranial to the level of the right renal vein showing a large thrombus in the IVC (black arrow). The left renal vein is normal (white arrow).

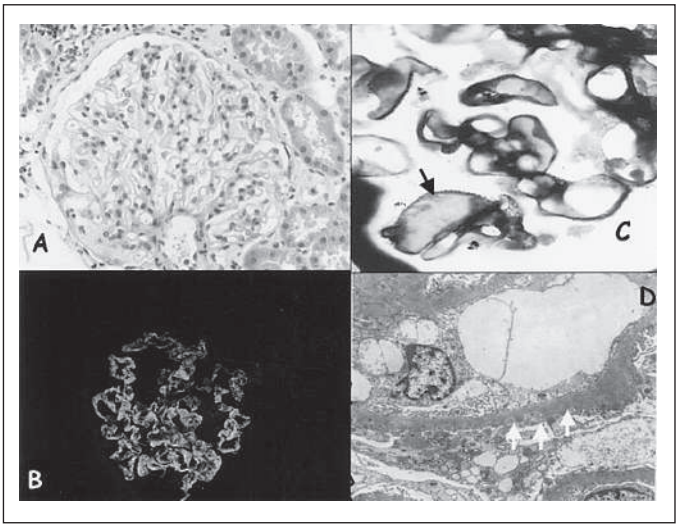

Figure 2: A) Glomerulus showing mild diffuse mesangial cell hyperplasia and diffusely thickened glomerular capillary wall (H.E. stain, original magnification). B) granular deposits of IgG along glomerular capillary wall at immunofluorescence; C) "Spikes" of glomerular basement membrane surrounded deposits (black arrow, methenamine silver); D) subepithelial electron–dense deposits (white arrows) at electron microscopy.

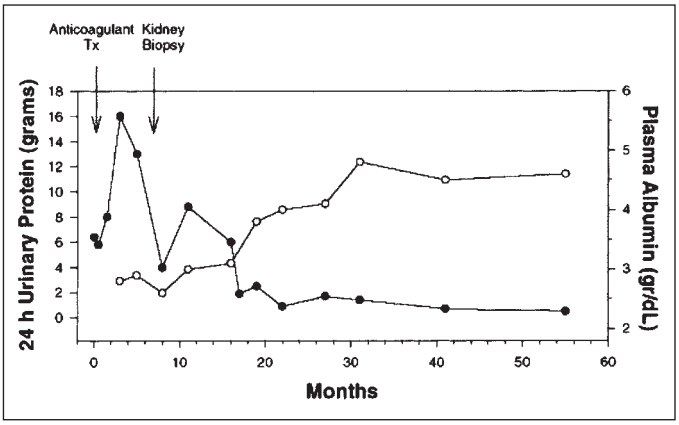

Figure 3: Urinary 24-hour protein secretion during 5 years of follow-up, showing marked improvement after administration of anticoagulants.

Table 1: Patient laboratory results at admission.

White Blood Cells (10^6/ml)	5.2
Hemoglobin (g/dl)	11.5
Platelets (10^6/ml)	173
Sodium (mM/l)	139
Potassium (mM/l)	4
Urea (mM/l)	2.6
Creatinine (mM/l)	62
Glucose (M/l)	5.7
Total protein (g/l)	62
Albumin (g/l)	24
Alanine Aminotransferase (units)	18
Lactate Dehydrogenase (units)	500
Total Cholesterol (mM/l)	7
HDL Cholesterol (mM/l)	1.03
LDL cholesterol (mM/l)	5
Triglicerides (mM/l)	2.06
International Normalized Ratio	1.19
Partial Thrombin Time (seconds)	38

explained the predisposition of patients with membranous glomerulopathy to RVT by the development of an immune complex-mediated hypercoagulable state in the renal venous system (6). The possibility that in some patients renal vein thrombosis initiates membranous glomerulopathy and proteinuria has thus been generally not accepted.

Nevertheless, the notion of RVT being a secondary phenomenon has been based on studies and reports that were conducted before the era of expanding understanding of thrombophillia. The series of discoveries in the last years of common inherited causes of procoagulant conditions, including APCR, hyperhomocysteinemia, PT210 mutation of prothrombin, and the antiphospholipid syndromes have not been recognized at that time. Our case report raises the possibility that, although most patients develop a hypercoagulable state secondary to nephrotic syndrome, in a minority of patients nephrotic syndrome may possibly be secondary to a hypercoagulable state, leading to renal vein thrombosis and a subsequent glomerulopathy. Alternatively, a second hypercoagulable disorder may serve as a 'second hit' and contribute to the development of renal vein thrombosis in patients with membranous glomerulopathy. A possible pathogenic linkage between renal vein thrombosis and an essential immune mediated nephropathy may be increased glomerular pressure in RVT leading to release of glomerular antigens and formation of an autoimmune reaction against them. This secondary bilateral autoimmune phenomenon has been suggested to occur even when renal vein occlusion is unilateral, although it could not be determined whether the membranous glomerulopathy was primary or secondary to the renal vein thrombosis (12). Recognition of inherited hypercoagulable disorders in patients with membranous glomerulopathy and renal vein thrombosis may carry important clinical implications, since prolonged anticoagulant treatment may be indicated in such cases. The described patient, who declined the use of immunomodulatory therapy, featured significant clinical improvement after a year of warfarin treatment. Although resolution of membranous glomerulopathy may have occurred spontaneously as occurs in some 30% of patients, a plausible possibility exists that this patient improved as a result of resolution of RVT. The major limitation of the suggested scenario, in which membranous glomerulopathy in the presented patient was caused by renal vein thrombosis due to hypercoagulability, is that it is solely based on the fact that the likelihood of these disorders occurring independently in the same patient is extremely low. The possibility that membranous nephropathy, renal vein thrombosis and factor V Leiden deficiency coincidentally coexisted in the same patient cannot be completely ruled out. Thus, this report cannot lead to any conclusion as to which is the cause and which is the effect. Only prospective studies can validate whether a true cause and effect relationship exists between these disorders. Until then, we suggest that physicians consider performing a full coagulation workup in patients with nephrosis and hypercoagulability, in order to rule-in or rule-out the coexistence of etiologic factors capable of causing thrombosis.

In conclusion, we raise the possibility that a unique subpopulation of patients might exist, in which inherited hypercoagulable disorders may predispose to the development of RVT in patients with membranous glomerulopathy or even contribute to the pathophysiology of membranous glomerulopathy. To test this hypothesis, we propose to conduct a systematic evaluation for the presence of the recently recognized inherited or acquired thrombophillic disorders in all patients with membranous nephropathy and nephrotic syndrome, especially those who develop RVT.

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Abbreviations

APCR: activated protein C resistance; PT: prothrombin time; PTT: partial prothrombin time; RVT: renal vein thrombosis.

References

1. Glassock RJ. Diagnosis and natural course of membranous nephropathy. Semin Nephrol 2003; 23: 324–32.
2. Dizon-Townson DS, Nelson LM, Jang H, et al. The incidence of the factor V Leiden mutation in an obstetric population and its relationship to deep vein thrombosis. Am J Obstet Gynecol 1997; 176: 883–6.
3. Juul K, Tybjaerg-Hansen A, Steffensen R, et al. Factor V Leiden: The Copenhagen City Heart Study and 2 meta-analyses. Blood 2002; 100: 3–10.
4. Heit JA, Sobell JL, Li H, et al. The incidence of venous thromboembolism among Factor V Leiden carriers: a community-based cohort study. J Thromb Haemost 2005; 3: 305–11.

5. Nickolas TL, Radhakrishnan J, Appel GB. Hyperlipidemia and thrombotic complications in patients with membranous nephropathy. Semin Nephrol 2003; 23: 406–11.
6. Rabelink TJ, Zwaginga JJ, Koomans HA, et al. Thrombosis and hemostasis in renal disease. Kidney Int 1994; 46: 287–96.
7. Llach F. Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. Kidney Int 1985; 28: 429–39.
8. Wagoner RD, Stanson AW, Holley KE, et al. Renal vein thrombosis in idiopathic membranous glomerulopathy and nephrotic syndrome: incidence and significance. Kidney Int 1983; 23: 368–74.
9. Pasquariello A, Camerini E. Unilateral renal vein thrombosis and pulmonary embolism complicating membranous nephropathy. Am J Nephrol 1992; 12: 134–6.
10. Alkjaersig N, Fletcher AP, Narayanan, et al. Course and resolution of the coagulopathy in nephrotic children. Kidney Int 1987; 31: 772–80.
11. Robert A, Olmer M, Sampol J, et al. Clinical correlation between hypercoagulability and thrombo-embolic phenomena. Kidney Int 1987; 31: 830–5.
12. Morrissey EC, McDonald BR, Rabetoy GM. Resolution of proteinuria secondary to bilateral renal vein thrombosis after treatment with systemic thrombolytic therapy. Am J Kidney Dis 1997; 29: 615-9.
13. Ozawa T, Boedecker EA, Schorr W, et al. Immune-complex disease with unilateral renal vein thrombosis. Arch Pathol Lab Med 1976; 100: 279–82.