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CASE REPORT

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The forgotten urinalysis: an integral part of unmasking thrombophilia

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ABSTRACT

A 43-year-old female presented with flank pain of two days duration. She had been admitted previously for bilateral lower extremity edema which had not improved with diuresis. Abdominal Imaging showed left ovarian vein thrombosis and left renal vein thrombosis extending into the IVC. Chest imaging revealed right lower lobe segmental pulmonary emboli. Careful review of serial urinalysis during previous admissions revealed significant proteinuria. Confirmatory urine tests followed by a renal biopsy led to a diagnosis of membranous nephropathy. We report a case of acute diffuse thromboembolism due to membranous nephropathy, unmasked by serial abnormal urinalysis.

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1. Background

Thrombus formation is typically characterized by a single or combination of three risk factors: endothelial damage, blood flow stasis, and or hypercoagulability [1,2]. Endothelial damage leads to exposure of the endothelium that can trigger the clotting cascade. Blood flow stasis results from immobility, which causes a larger than normal accumulation of clotting factors. Hypercoagulability can take place due to syndromes such as primary thrombophilia, or secondary to syndromes such as nephrotic syndrome [3]. In patients with nephrotic syndrome, there is a loss of anticoagulant clotting factors in the urine [3]. Such loss leads to greater than normal clotting, resulting in thrombus formation [3].

2. Case presentation

A 43-year-old female with history of uterine fibroids and recurrent nephrolithiasis presented with complaints of worsening, 'stabbing' flank pain of two days duration. She had associated symptoms of nausea, vomiting, and dysuria. She reported using oral contraceptive pills for several months, stopping four months prior to presentation. She denied any abnormal bleeding related to the fibroid and reported no pelvic pressure or pain. Family history was positive for thromboembolic disease, but negative for renal disease. She was seen in the emergency room three weeks prior for complaints of worsening bilateral lower extremity edema. Prior to the emergency room visit, she was seen in the primary care clinic and had been given a loop diuretic without improvement. Bilateral lower extremity Dopplers in the emergency room on the prior presentation revealed no evidence of deep vein thrombosis, and she was discharged.

Laboratory studies including complete blood count and comprehensive metabolic panel were unremarkable. Lipid panel revealed total cholesterol 293 mg/dL (high), non-HDL cholesterol 207 mg/dL (high).

Computed Tomography Angiography (CTA) of the chest displayed right lower lobe segmental pulmonary emboli without evidence of increased right heart pressures.

Computed Tomography (CT) of the abdomen and pelvis displayed hyperdensity and distention of the left renal vein as well as renal and ovarian vein thrombosis.

CT venous of the abdomen and pelvis showed an acute nonocclusive left renal vein thrombosis that extended to the IVC cephalad approximately 11 mm, a near occlusive thrombus of the proximal left ovarian vein, nonocclusive thrombi within a few distal left uterine veins, left sided pyelitis, and a large left sided uterine myometrial fibroid measuring 9.2 × 5.8 cm (Figures 1–2)

Patient was started on Lovenox 1 mg/kg q 12 hour and transferred to PCU for close monitoring.

Lower extremity venous Doppler displayed no evidence of acute deep or superficial thrombosis.

Urinalysis performed showed 3+albumin, as well as a 24-hour urine protein amount of 11,610 mg/dl. 24-hour Urine protein/creatinine ratio was found to be 8.25 at the most recent testing, with values ranging around 12–15 in the past months during recent admissions. In light of nephrotic range proteinuria, a kidney biopsy was performed.

Staining for phospholipase A2 receptor (PLA2R) was found to be negative within the glomerular deposits,

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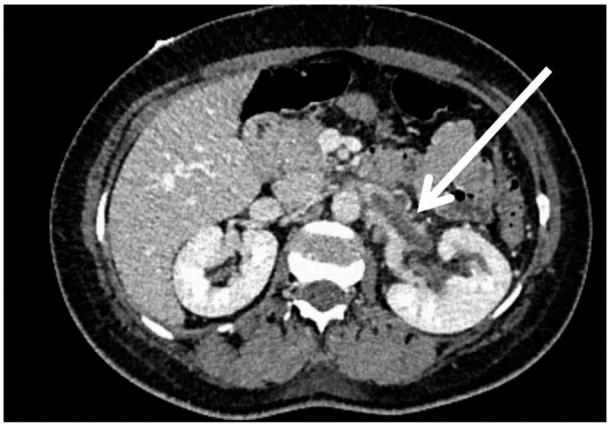

Figure 1. Axial view displaying left renal vein thrombosis.

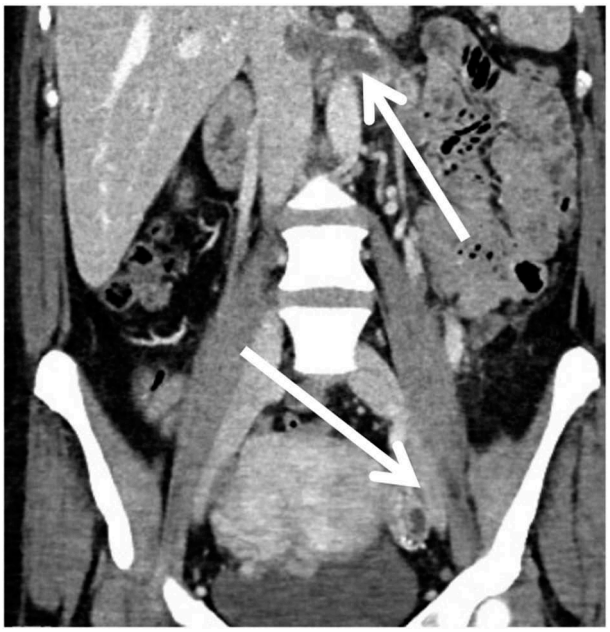

Figure 2. Coronal view displaying thrombosis in the renal vein with further extension into the inferior vena cava (top arrowhead). Also displayed is the ovarian vein clot (bottom arrowhead).

raising the possibility of a secondary membranous glomerulopathy (Figure 3). Immunofluorescence displayed a diffuse granular capillary loop reaction for IgG (3+), C3 (2+), kappa light chain (3+), and lamba light chain (2+) (Figure 4). Kappa and lambda stains were equal throughout the interstitium and tubular casts.

Electron microscopy displayed thickened capillary loops by the presence of numerous electron dense deposits associated. There was mild adjacent basement membrane response with some intramembranous deposits noted. Ultrastructural examination shows diffuse effacement of podocyte foot processes (Figure 5).

3. Discussion

Nephrotic syndrome is characterized by decreased ability of the glomerulus barrier to prevent the filtration of proteins of intermediate size (40–200 kDa) as

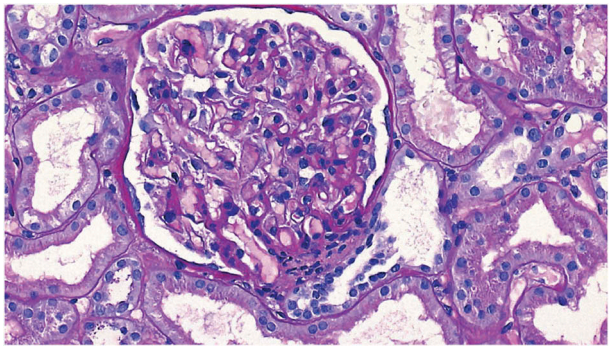

Figure 3. Normal glomerulus without proliferative changes (Periodic acid-Schiff, original magnification x 400).

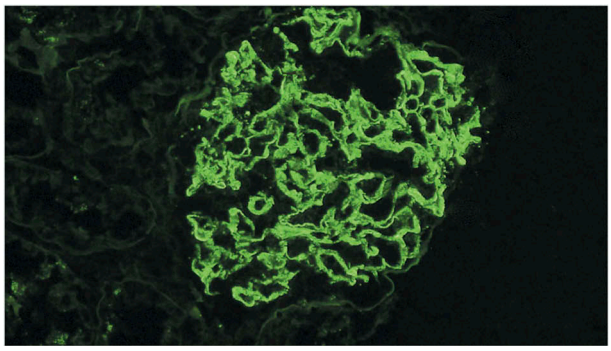

Figure 4. Glomerulus with granular capillary loop staining for IgG (direct immunofluorescence; original magnification × 400).

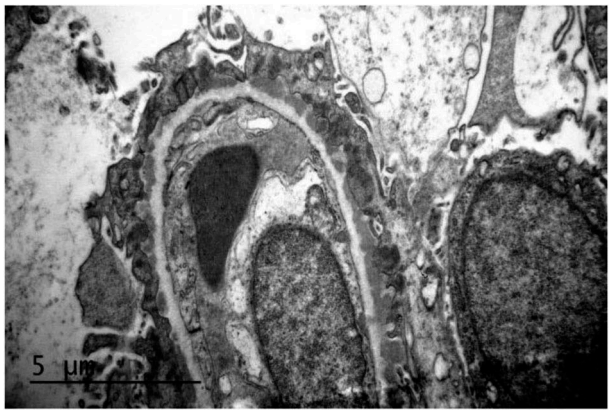

Figure 5. Glomerular basement membranes with subepithelial electron dense deposits (original magnification × 12,000).

well as other macromolecules from the urine [4]. Such substances that are lost in the urine include albumin, immunoglobulins, hormones, and proteins that are involved with the clotting cascade [5,6]. Clinical symptoms associated with nephrotic syndrome include abnormal lipid profiles, edema, hypoalbuminemia, and hypercoagulability [4]. One of the most serious, but often not considered, consequences of nephrotic syndrome is thromboembolism, as was seen in our patient [7]. This increased coagulation is a result of small proteins that are lost in the urine due to nephrotic syndrome, specifically

antithrombin III, protein C and S [4]. However, procoagulants are not as affected because of their high molecular weight, which prevents these proteins from being filtered into the urine as well [4].

The hypercoagulable state produced by nephrotic syndrome is produced through the increased level of platelets, fibrinogen, factor V, combined factors 8 and 10, and increased activation of Hageman factor that have been documented in patients with nephrotic syndrome [8,9]. These factors are increased due to the synthesis of proteins that takes place by the liver to attempt to compensate for the other factors that are being lost [10]. This is further complicated by the loss of antithrombin III levels that takes place in the urine, which has its importance in stopping clotting proteases [11].

Hypercoagulability is one of the three factors involved in thrombosis formation, also known as Virchow's triad [10]. The other two factors involve endothelial damage and stasis [10]. Endothelial damage takes place due to vessel wall damage, while stasis is characterized due to the slowing down of blood flow [10].

In 1840, Rayer [12] detailed cases of renal vein thrombosis, some of which had clinical features of underlying nephrotic syndrome. In 1939, Derow [13] then described a case of nephrotic syndrome with subsequent complications of chronic thrombosis of the renal vein and inferior vena cava. After these case reports, many reports have further documented the association of nephrotic syndrome as well as renal vein thrombosis [8,14]. Initially, it was believed that nephrotic syndrome took place due to the renal vein thrombosis [1]. This has been since discredited due to documented reasons such as inducing renal vein thrombosis leads to only mild proteinuria, renal vein thrombosis that has been documented without nephrotic syndrome, as well as renal vein thrombosis that has been shown to occur after the onset of nephrotic syndrome [1]. Such cases thus described the association that nephrotic syndrome leads to renal vein thrombosis, rather than causing it [1].

Kang and Park [8] discussed three cases in which renal vein thrombosis was diagnosed in well-established nephrotic syndrome patients. These patients had been diagnosed with nephrotic syndrome previously, and acutely presented with right or left sided flank pain that had been taking place on average for two days. All of these patients had gotten a urinalysis as part of their routine work up as a nephrotic syndrome patient, with the urinalysis showing 3+ protein in all three patients. Further testing in these patients showed hypodense lesions in the renal vein, with renal venography showing renal vein thrombosis. Yamashita [15] also discussed a similar case report for a 54-year-old woman undergoing steroid treatment for nephrotic syndrome. After she developed right lower quadrant pain, a CT scan displayed thrombosis of the right ovarian vein [15]. The conclusion drawn by this case was that when any patient with established nephrotic syndrome complains of abdominal pain, a primary consideration should be venous thrombosis [15].

In general, thromboses of abdominal veins that are outside the iliac-caval axis are not common, but when such thromboses do occur they are clinically relevant [16]. Renal vein thrombosis has been shown to have numerous etiologies, but one of the most common causes has been shown to be nephrotic syndrome [1]. Renal vein thrombosis has been shown in many accounts to have an association with membranous glomerulopathy mainly, but less frequently in other forms of glomerulopathy such as membranoproliferative [8]. Thromboembolic consequences are more likely when the underlying nephrotic syndrome is taking place due to membranous nephropathy. The exact pathogenic mechanism of this association is not known, but it has been well established that the hypercoagulable state produced by nephrotic syndrome further increases the risk of renal vein thrombosis [8]. Specific reasons as to why the renal vein is more susceptible to thrombosis is unclear [1]. In fact, though the thromboembolic consequences of nephrotic syndrome can involve both the venous and arterial sides of the systemic circulation, it is has been found that arterial thrombosis is a less common occurrence than venous thrombosis, but the exact reasoning behind this as well is unknown [4].

Epidemiology shows variability of the presence of renal vein thrombosis in patients with nephrotic syndrome, ranging from 5–62% [1]. Age is related to the presence of renal vein thrombosis as far as age is related to the risk of glomerular disease [1]. For example, membranous nephropathy is the most common cause of nephrotic syndrome in adults, as well as the type of glomerular disease most commonly associated with renal vein thrombosis, and as such renal vein thrombosis is more common in adults [1]. In terms of gender, membranous nephropathy is more common in males with a ratio of 2:1, and by correlation there may be a male predilection for renal vein thrombosis [1].

Nephrotic syndrome patients with unilateral renal vein thrombosis who are asymptomatic may not require treatment so long as they are asymptomatic [10]. It is, however, important to maintain active surveillance with these patients, as well as advocate for changes in diet to minimize proteinuria by decreasing salt and protein [10]. The patient's progress and condition will determine if other interventions such as angiotensin converting enzyme inhibitors, angiotensinogen II receptor blockers, cyclosporine, or corticosteroids are necessary [10].

Other important considerations of abdominal vein thromboses should include ovarian vein thrombosis. As described in a case report by Yamashita [15], a female patient was undergoing steroid treatment for remission for minimal change nephrotic syndrome [15]. She presented with pain in her right lower abdomen, and a CT scan of the abdomen displayed thrombosis of the right ovarian vein [15]. Female patients with nephrotic syndrome who present with pelvic pain should undergo diagnostic workup for ovarian vein thrombosis, especially if the patient has established deep vein thrombosis of other veins as well [15]. This is an important consideration especially on the left side due to the anatomy of the venous system. The left ovarian vein drains into the left renal vein, which then drains into the inferior vena cava [15]. If further symptoms progress to include shortness of breath, this could indicate a possible pulmonary embolism that has further progressed from the ovarian vein [15].

Pulmonary embolisms are also a relevant consideration in patients with nephrotic syndrome [17]. Such emboli can progress from a renal or ovarian vein thrombosis that dislodge and further travel to the pulmonary system. The concern with PE is the asymptomatic nature in most patients, and as such in general a low threshold for diagnostic work up in addition to a high index of suspicion should always be patient [17]. Advances in knowledge have determined that around 35% of patients with nephrotic syndrome had a pulmonary embolism following further work up [18]. In fact, thromboembolic complications are one of the most important extrarenal complications that can take place for patients with nephrotic syndrome [19]. Considering all of this information, it is likely that the actual amount of PE in patients with nephrotic syndrome is much higher than the value that is actually reported, and as such is underdiagnosed [17].

Patients who are symptomatic, such as our patient, should have anticoagulation to prevent further progression of the thrombus [10]. Anticoagulation is begun with heparin, with treatment then transitioning to warfarin [10]. As described in a case report by Wang [20] also involving a female patient with membranous glomerulonephritis who then progressed to having renal vein thrombosis and pulmonary embolism, her condition was successfully managed with the use of low molecular weight heparin [20], Low molecular weight heparin use in nephrotic syndrome patients appears to be safe and also effective for managing thromboembolism [20]. The duration of this therapy would vary, with a wide range of potential treatment options varying from year to lifelong depending on the patient and symptoms [10]. Another important factor to consider for prognosis in such patients is the level of albumin [10]. If the serum albumin levels are below 2.5 grams/L, it is recommended for patients to be treated with anticoagulation [10]. In such instances, it is then advised to continue the anticoagulation until the nephrotic syndrome has resolved [21].

4. Conclusion

There is immense benefit of performing a urinalysis when evaluating a patient with symptoms of a thrombus. As in our case, if our patient had a urinalysis performed alongside the other laboratory tests that were performed, this would have more correctly directed the diagnosis toward nephrotic syndrome. Upon consideration of the 3+ protein in our patient's urinalysis, the appropriate conclusion was drawn that thrombus formation was provoked by loss of clotting factors in the urine. Urinalysis is an underutilized test in the examination of patients with thromboembolism, and is often overshadowed by tests for genetic factors. Performing urinalysis, a quick and noninvasive test may decrease the time to correct diagnosis of patients with nephrotic syndrome, presenting with thromboembolism.

Disclosure statement

No potential conflict of interest was reported by the authors.

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