CLINICAL VIGNETTE

Pulmonary Embolism Prompts Diagnosis of Nephrotic Syndrome

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Introduction

Hypercoagulability is a serious sequela of nephrotic syndrome (NS) that can cause life-threatening thromboemboli. We describe a patient presenting with an apparent unprovoked pulmonary embolism (PE) who was later diagnosed with nephrotic syndrome. Unfortunately, poor access to care and ineffective care coordination complicated treatment.

Case

A 58-year-old man with no known medical conditions presented to a public safety-net emergency department with acute right-sided pleuritic back pain, hemoptysis, and dysuria. He also reported four months of initially intermittent bilateral lower extremity edema that became persistent in the prior week. Vital signs included tachypneic up to 27 breaths per minute, BP of 144/92 and room air oxygen saturation of 93-96%. Examination was remarkable for right lower pulmonary crackles and bilateral lower extremity pitting edema. Laboratory results were notable for hypoalbuminemia (1.7 g/dL), creatinine of 1.2 mg/dL without prior baseline, and urinalysis with significant proteinuria of 600 mg/dL. Computed tomography pulmonary angiography revealed an acute right lower lobe PE with moderate right pleural effusion. Lower extremity venous duplex ultrasound did not show thrombosis. He was started on therapeutic enoxaparin and admitted for management and coordination of anticoagulation.

Initial history did not identify a provoking factor for his PE. However, after noting hypoalbuminemia and proteinuria, Nephrotic Syndrome (NS) was suspected. Subsequent random urine protein to creatinine ratio revealed nephrotic-range proteinuria of 8.2 mg/mg. After nephrology consultation, he was discharged on rivaroxaban and losartan. One week later, serologic analysis resulted positive for phospholipase A2 receptor (PLA2R) antibodies, consistent with primary membranous nephropathy. Immunosuppressive therapy was delayed because the patient was found to have latent tuberculosis infection (LTBI). Difficulty accessing subspecialty and primary care delayed initiation of LTBI treatment and initiation of immunosuppressive therapy. Nearly three months after initial presentation, the patient traveled to his home country for urgent family matters prior to coordination of treatment for LTBI or membranous nephropathy. To date, he has not reconnected with care.

Discussion

Hypercoagulability is a known sequelae of NS, leading to increased risk for intravascular thrombosis and embolism. In one matched cohort study, patients with NS had a 7.7% and 14.0% 10-year absolute risk of venous and arterial thromboembolic events.[1] The relative risk of developing venous thromboembolism (VTE) was 7.1% and arterial thromboembolism was 3.1% within one year after NS diagnosis compared to those without NS.[1] Individuals with membranous nephropathy, one of the most common causes of nephrotic syndrome, have an even greater risk for VTE compared with other causes of nephrotic syndrome.[2,3] Though VTE is a relatively common complication of NS, patients are more likely to present with other symptoms, including edema, dyspnea, or fatigue. Hypertension, proteinuria, hypoalbuminemia, and hyperlipidemia are other common findings and less than 1% of patients with primary membranous nephropathy initially present with thromboembolism.[4,5]

Both systemic diseases and medications can damage the glomerular membrane and lead to nephrotic syndrome. Primary membranous nephropathy is an autoimmune disease characterized by autoantibodies that target podocyte antigens. This leads to immune complex deposition in the glomerular basement membrane and complement-mediated podocyte injury. PLA2R is the most commonly targeted podocyte antigen in primary membranous nephropathy, occurring in about 70% of cases.[6] Compromise of the glomerular filtration barrier results in inappropriate glomerular protein filtration and excretion in the urine. Loss of anticoagulation factors including protein S and antithrombin contribute to the hypercoagulable state in NS. Additionally, increased platelet activity and elevated levels of procoagulant factors are found in patients with NS.[4]

In our patient, a urinalysis and complete metabolic panel ordered in the emergency room detected heavy proteinuria and hypoalbuminemia, prompting further evaluation for nephrotic syndrome. These two commonly-ordered tests can be used to screen for nephrotic syndrome when evaluating thromboembolic events. One study found urine dipstick to have low sensitivity (55.6%) but high specificity (92.4%) for proteinuria, suggesting formal urinalysis is a superior screening tool.[7] Dwyer *et al*. reached a similar conclusion, recommending follow-up random urine protein to creatinine ratio after negative

dipstick when screening for proteinuria in pregnancy.[8] Nephrotic-range proteinuria can be formally identified and quantitated with 24 hour urinary protein measurement or by the more convenient urine protein to creatinine ratio.[9] Hypoalbuminemia which is present in many conditions, is not a sensitive marker, but is a fundamental characteristic of nephrotic syndrome.[9,10] Though case reports emphasize the utility of urinalysis and serum albumin analysis in investigating NS,[11-13] no studies were found that formally evaluate the sensitivity of hypoalbuminemia and proteinuria (on urinalysis) combined to screen for nephrotic syndrome. Further work could investigate cost-effectiveness and impact on morbidity and mortality of screening, follow-up testing, and early treatment.

Patients with active nephrotic syndrome, especially those with low serum albumin (<2.0 g/dL), are in a constant hypercoagulable state. They often require indefinite secondary prevention with anticoagulation therapy.[14] To further reduce our patient's risk of repeat VTE, he should have received treatment for his underlying condition. Active membranous nephropathy, evidenced by detectable serum anti-PLA2R, warrants immunosuppressive therapy with steroids, calcineurin inhibitors, rituximab, or a combination of these drugs.[5] Prior to immunosuppression, patients must be tested for latent tuberculosis and if positive, receive treatment to avoid disease activation.

Prior case reports identified patients diagnosed with nephrotic syndrome after presenting with VTE, often PE. In some, diagnosis of NS was made after weeks in the hospital or multiple emergency room visits despite lab findings of hypoalbuminemia and proteinuria on the initial encounter.[11,15] Many describe treatment with corticosteroids, either empirically or after kidney biopsy.[12,16,17] Ahmed and Saeed presented a 42-year old man with pulmonary embolism and subsequent biopsy-proven membranous glomerulonephritis. He did not consistently take his prescribed anticoagulant or prednisone and unfortunately presented two years later with right middle cerebral artery thrombosis and gross proteinuria.[18] This illustrates one of many potential complications from inadequately treated nephrotic syndrome, that we fear may affect our patient. A literature review did not identify any publications discussing patients with steroid-sensitive NS whose treatment was delayed due to LTBI. Our patient faced this challenge that delayed his treatment for membranous nephropathy.

Our patient was lost to follow-up before he could start treatment for LTBI or immunosuppressive therapy. Nearly three months after hospital discharge, the patient's Medicaid application was still processing, and he did not have an assigned primary care provider to treat his latent tuberculosis. Our patient is not alone in facing challenges accessing primary care. A Northern California study reported only 19% of primary care offices with appointments available within 10 business days, with median wait times from 7 to 32 days. Limited access to primary care results in increased emergency room utilization and higher five-year mortality rates.[18,19] Immigrants and migrant workers are also more likely to be lost to follow-up.[20,21] Our patient waited 75 days before traveling out of the country for urgent family matters. Although he has been assigned a primary care provider, we have not been able to reconnect with him. With ongoing NS, he is at risk of recurrent thromboembolism, cardiovascular complications, and progressive renal failure.[22,23]

Conclusion

This case highlights the importance of taking into account all laboratory values during clinical problem-solving. Patients with unexplained thromboembolism, can be easily screened for NS by checking serum albumin and urinalysis. Although NS is an uncommon cause of thromboembolism, early consideration can lead to quicker diagnosis and treatment, reducing serious complications. This patient had prompt diagnosis of NS despite atypical presentation with a PE. Unfortunately his treatment hindered by financial and systemic barriers to care. Proactive care coordination and swift follow-up is needed for patients to receive the proper medical therapy.

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