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ACUTE ISCHEMIC STROKE AS A PRESENTING FEATURE OF PRIMARY MEMBRANOUS NEPHROPATHY: A RARE AND UNDER-RECOGNIZED ASSOCIATION

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ABSTRACT **Background:** Nephrotic syndrome is classically associated with venous thromboembolism, but arterial events such as ischemic stroke remain rare and under-recognized. Primary membranous nephropathy (PMN) is a common cause of nephrotic syndrome in adults; however, cerebrovascular events seldom constitute the initial presentation. **Case Presentation:** A 42-year-old man, chronic smoker and alcohol user with no prior comorbidities, presented with acute slurred speech and right-sided hemiparesis. Neuroimaging revealed a left middle cerebral artery infarct with complete occlusion of the left internal carotid and middle cerebral arteries. Laboratory evaluation showed severe hypoalbuminemia (1.8 g/dL), nephrotic-range proteinuria (6.3 g/day), and strongly positive anti-PLA2R antibody (276.6 RU/mL), confirming PMN. Hypercoagulability work-up demonstrated reduced antithrombin III and markedly elevated fibrinogen. Secondary causes of nephrotic syndrome were excluded. The patient was initiated on high-dose corticosteroids and planned for the modified Ponticelli regimen alongside standard stroke management. **Conclusion:** This case highlights ischemic stroke as a rare but serious initial manifestation of PMN.Nephrotic syndrome should be considered in young patients presenting with stroke, especially in the absence of conventional vascular risk factors. Early recognition and treatment of the underlying renal disease are critical for improving outcomes.

KEYWORDS : Nephrotic Syndrome; Membranous Nephropathy; Ischemic Stroke; Hypercoagulability; Anti-PLA2R Antibody

INTRODUCTION

Nephrotic syndrome (NS) is characterized by heavy proteinuria (>3.5 g/day), hypoalbuminemia, hyperlipidemia, and edema. Venous thromboembolism is a well-established complication of NS; however, arterial thrombotic events are less common and often under-appreciated in clinical practice.[1,2] Several recent reviews and cohort studies confirm that both venous and arterial thromboembolic events occur in NS and that clinicians should maintain a high index of suspicion when patients present with atypical thrombotic events.

Primary membranous nephropathy (PMN) is marked by subepithelial immune deposits[3,4,5] and circulating anti-phospholipase A2 receptor (PLA2R) antibodies in many patients; PLA2R positivity correlates with disease activity and prognosis. Emerging evidence suggests anti-PLA2R seropositivity [6,7] (and higher titers) may also be associated with an increased risk of thrombotic complications in PMN.

We present a case in which acute ischemic stroke was the presenting manifestation of PMN to highlight the need for vigilance for nephrotic syndrome in young stroke patients without an obvious cardio- or atherosclerotic source.

Case Report

A 42-year-old male, chronic smoker and alcohol user, presented with sudden-onset slurred speech and right-sided weakness. There was no prior history of hypertension, diabetes mellitus, or known cardiovascular disease. Neurological examination revealed right hemiparesis and dysarthria.

Neuroimaging: Non-contrast CT of the brain revealed acute infarction involving the left frontoparietal and temporal lobes with capsuloganglionic involvement and midline shift. CT angiography confirmed complete occlusion of the left internal carotid artery (ICA) and middle cerebral artery (MCA).

Laboratory Investigations: Renal function was preserved (serum creatinine 0.8 mg/dL). Serum albumin was 1.8 g/dL with total protein 4.1 g/dL. Inflammatory markers were elevated (ESR 87 mm/hr, CRP 34.6 mg/dL). Twenty-four-hour urine protein excretion was 6.3 g/day and urine protein/creatinine ratio was 10.4. Urinalysis showed microscopic hematuria and granular casts. Echocardiography showed preserved LV function without thrombus or vegetations. Serology revealed strongly positive anti-PLA2R antibody (276.6 RU/mL); ANA, HBsAg, HCV, HIV, and routine malignancy markers were negative. Hypercoagulability testing demonstrated reduced antithrombin III (65%) and markedly elevated fibrinogen (788 mg/dL), with normal protein C and S, and negative antiphospholipid antibodies. Mild hyperhomocysteinemia (17.8 µmol/L) was present. Details of laboratory investigations are depicted in Table 1.

Table 1: Laboratory Investigations-Baseline Blood Work up

Investigation	Value	Reference Range
Hemoglobin	16.3 g/dL	13–17 g/dL
RBC Count	4.77 mil/uL	4.5–5.5 mil/uL
Hematocrit (HCT)	47%	40–50%
Total Leucocyte Count	9900/uL	4000–10,000/uL
Neutrophils	78%	40–80%
Lymphocytes	14%	20–40%
Monocytes	4%	2–10%
Eosinophils	4%	1–6%
Platelet Count	2.92 lakh/uL	1.5–4.5 lakh/uL
Random Blood Sugar	92 mg/dL	70-110 mg/dL
Urea	33 mg/dL	15–45 mg/dL
Creatinine	0.8 mg/dL	0.6–1.3 mg/dL
Sodium	137 mEq/L	135–145 mEq/L
Potassium	4.2 mEq/L	3.5–4.5 mEq/L
Total Protein	4.1 g/dL	5.5–8.0 g/dL
Albumin	1.8 g/dL	3.5–5.0 g/dL
ESR	87 mm/hr	0–14 mm/hr
CRP	34.6 mg/dL	0–6 mg/dL
Urine Protein/Creatinine Ratio	10.4	<150 mg/g
24 hr Urine Protein	6300 mg	<150 mg/day

Given the nephrotic-range proteinuria, severe hypoalbuminemia, and high anti-PLA2R titer, a diagnosis of primary membranous nephropathy was made.

Management and Course: The patient received standard ischemic stroke care (antiplatelet therapy, statin, supportive neurocritical care when indicated) and rehabilitation. High-dose corticosteroid therapy was started and the patient was planned for the modified Ponticelli regimen/definitive immunosuppression. Renal biopsy was deferred/(based on clinical practice and patient consent) since anti-PLA2R positivity with nephrotic-range proteinuria is highly suggestive of PMN.

DISCUSSION

Nephrotic syndrome creates a multifactorial hypercoagulable state [1,2,8], urinary loss of natural anticoagulants (particularly antithrombin III), increased hepatic synthesis of procoagulant proteins such as fibrinogen and factors V/VIII, platelet hyperreactivity, and reduced fibrinolytic activity. These mechanisms collectively increase the risk

of both venous and arterial thrombotic events. Contemporary reviews emphasize that while venous thromboses remain more frequent, arterial events — including ischemic stroke and myocardial infarction — are clinically meaningful and may be the presenting manifestation in some patients.

Large cohort and registry studies have shown that patients with NS have increased rates of arterial thromboembolic events compared with the general population, and stroke is a recognized complication.[9,10,11] Recent dedicated analyses of ischemic stroke in NS report variable presentations,[12,13] from small cortical infarcts to large-vessel occlusions similar to our patient. These contemporary clinical descriptions reinforce the necessity of investigating renal causes in young or otherwise unexplained stroke presentations.

Regarding PMN specifically, several recent studies demonstrate an association between anti-PLA2R positivity (and higher titers) and thrombotic risk, likely reflecting that higher antibody levels indicate active, heavy proteinuria and prolonged disease activity — both contributors to coagulation imbalance. [5,6,7]This biological plausibility, together with accumulating case reports of stroke associated with PMN, supports the link observed in our patient.

Therapeutically, immunosuppression to control the underlying glomerular disease reduces proteinuria and should diminish the prothrombotic milieu. Contemporary treatment paradigms for PMN increasingly favor anti-CD20 therapy (rituximab) alongside or instead of traditional cyclophosphamide/steroid regimens in many settings,[14] but modified Ponticelli and other regimens remain in use depending on patient characteristics and resource availability. Decisions about anticoagulation (prophylactic or therapeutic) in NS remain individualized[15]; recent reviews stress weighing thrombotic risk (albumin, severity of proteinuria, prior thrombosis) against bleeding risk and patient comorbidities.

CONCLUSION

Ischemic stroke can, albeit rarely, be the initial manifestation of primary membranous nephropathy. Early recognition of nephrotic syndrome in young stroke patients without conventional vascular risk factors-through simple laboratory screening (serum albumin, urine protein)-can prompt investigations for PMN (including anti-PLA2R) and allow timely initiation of disease-directed therapy to reduce the risk of recurrent thrombotic events. Clinicians should maintain a low threshold for renal evaluation in atypical stroke presentations.

Declarations

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Patient Consent: Written informed consent was obtained for publication.

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