



Phospholipase A2 Receptor-Positive Membranous Nephropathy Associated with Polycythemia Presenting with Recurrent Venous Thrombosis

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ABSTRACT

Background: Nephrotic syndrome with concomitant polycythemia is exceedingly rare, and its association with phospholipase A2 receptor (PLA2R)-positive membranous nephropathy is even more uncommon.

Case Presentation: We report the case of a 29-year-old male who presented with recurrent venous thromboembolic events, including pulmonary embolism and renal vein thrombosis, and was subsequently found to have PLA2R-positive membranous nephropathy with secondary polycythemia. Despite anticoagulation and immunosuppressive therapy, the patient continued to have recurrent thrombotic episodes and persistent proteinuria, ultimately requiring escalation to a modified Ponticelli regimen. This case underscores several important learning points. First, polycythemia as a manifestation of membranous nephropathy is an extremely rare phenomenon, with only a handful of cases described in the literature. Second, the presence of recurrent thromboembolism in young patients warrants careful evaluation for underlying glomerular disease, particularly when associated with heavy proteinuria and hypoalbuminemia. Third, the pathophysiological link between nephrotic syndrome and secondary polycythemia remains unclear, highlighting the need for ongoing clinical vigilance and further research.

Conclusion: This report adds to the limited literature on the coexistence of membranous nephropathy and polycythemia, while emphasizing the importance of early recognition, combined immunosuppressive and anticoagulant strategies, and close follow-up to reduce morbidity from thrombotic complications.

KEYWORDS: Polycythemia; PLA2R antigen; Membranous nephropathy; Venous embolism

INTRODUCTION

Nephrotic syndrome is a clinical entity characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema, and is frequently associated with complications such as infections, thromboembolic events, and cardiovascular morbidity. While secondary systemic associations such as diabetes mellitus, systemic lupus erythematosus, and infections are well-recognized, hematological abnormalities are relatively less common. Among these, polycythemia occurring in the setting of nephrotic syndrome is extremely rare and has only been described sporadically in the literature.

Within the spectrum of glomerular diseases, membranous nephropathy (MN) is one of the leading causes of nephrotic syndrome in adults. The identification of autoantibodies against phospholipase A2 receptor (PLA2R) has helped distinguish primary MN from secondary forms. Although MN has been associated with complications such as venous thromboembolism due to its nephrotic state, the occurrence of concomitant polycythemia with PLA2R-positive MN is exceptionally uncommon, with very few reported cases worldwide.

Polycythemia is defined as hemoglobin (Hb) more than 16.5 g/dL in males and 16 g/dL in females or hematocrit more than 49% in males and 48% in females (WHO 2016) [1]. Renal conditions that increase renal mass and stimulate excess erythropoietin (EPO) production are more typically associated with secondary polycythemia, such as renal tumors, bi

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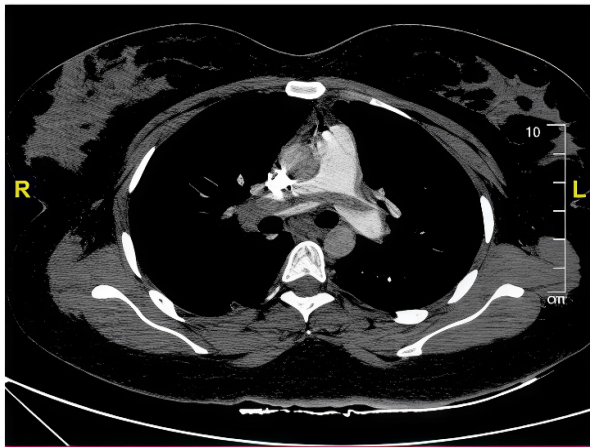


Figure 1: CT pulmonary angiogram revealed wedge shaped opacity in pulmonary artery suggestive of pulmonary thromboembolism.

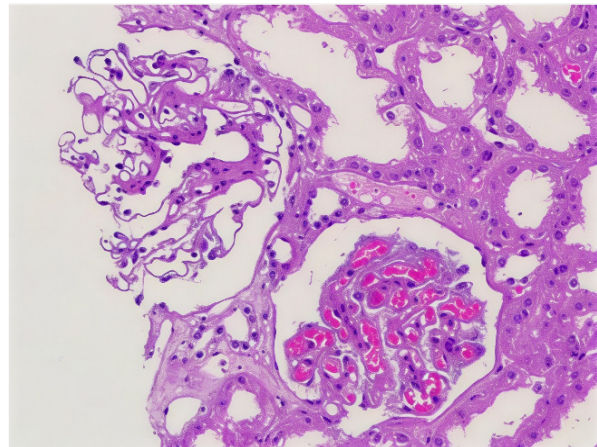


Figure 2: Light microscopy (PAS stain) showed diffuse GBM thickening and intramembranous mottling.

lateral hydronephrosis, polycystic kidney disease, post-transplantation states, renal artery stenosis, and Bartter syndrome. However, its association with nephrotic syndrome—particularly membranous nephropathy—has been described only rarely [2], first reported by Emanuel *et al* [3].

We report a case of PLA2R-positive membranous nephropathy complicated by secondary polycythemia and recurrent venous thrombosis, a unique presentation that adds to the very limited existing literature.

CASE PRESENTATION

A 29-year-old male, non-diabetic and non-hypertensive, presented with complaints of frothy urine for one year and intermittent leg swelling for eight months, along with acute shortness of breath for one day.

Past Clinical Events: One year earlier, he developed loose stools requiring hospitalization and fluid resuscitation. Subsequently, he experienced sudden-onset chest pain, shortness of breath, and loss of consciousness. A CT pulmonary angiogram revealed pulmonary thromboembolism (Fig. 1), for which he was thrombolysed with alteplase and discharged on oral apixaban. He remained asymptomatic for two months with good compliance, but then developed another episode of shortness of

breath, again diagnosed as pulmonary embolism, and managed with enoxaparin.

Clinical Evaluation: At the time of nephrology referral, he had insidious, gradually progressive bilateral lower limb edema up to the knees (symmetrical, non-tender, without skin changes).

Laboratory Investigations:

Hematology: Hb 18.5 g/dL, PCV 56%, WBC 8900/μL, platelets 2.1 lakh/μL.

Biochemistry: Urea 23 mg/dL, creatinine 0.67 mg/dL, normal LFTs, hypoalbuminemia (2.15 g/dL), normal lipid and thyroid profile.

Urine: Albumin ++, RBCs 15–20/hpf, UPCR 10.73, 24-h urine protein 10.6 g.

Immunology: ANA, ENA, C3, C4, c-ANCA, p-ANCA, and anti-PLA2R antibody were initially negative.

Other workup:

Polycythemia evaluation: JAK2 exon and V617F mutations, BCR-ABL, MPL, CALR mutations all negative; serum EPO normal; bone marrow biopsy showed mild erythroid hyperplasia.

Thrombophilia profile: Antithrombin III 70% (slightly low), protein C, protein S, and

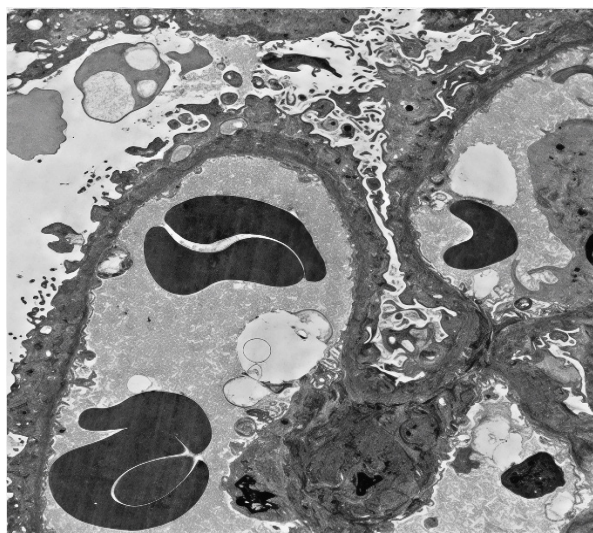


Figure 3: Electron microscopy confirmed stage III membranous nephropathy.

homocysteine normal; MTHFR mutation negative.

APLA screen: Negative.

Imaging:

USG abdomen: Mildly bulky kidneys with preserved corticomedullary differentiation.

2D echocardiography: Dilated right atrium and ventricle.

Initial Management: In view of high PCV, therapeutic phlebotomy was performed. He was started on oral prednisolone (1 mg/kg) plus apixaban. Despite eight weeks of therapy, proteinuria persisted (UPCR 10.73), so tacrolimus was added.

Kidney Biopsies:

First biopsy: Non-proliferative glomerulonephritis with focal vacuolar changes.

Repeat biopsy: PLA2R-positive membranous nephropathy, stage 3 (Fig. 2 & Fig. 3), confirmed on light microscopy, immunofluorescence (IgG1/4, C3), and PLA2R immunohistochemistry. Anti-PLA2R antibody was rechecked and strongly positive (91 RU/ml).

Subsequent Course: He was treated with rituximab (1 g IV on day 0 and 14) along with

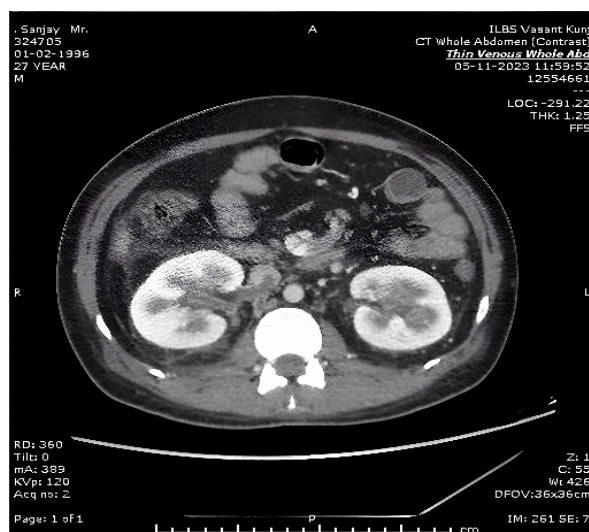


Figure 4: CT angiography showed right renal vein thrombosis with IVC extension.

anticoagulation. PCV was monitored, with repeat therapeutic phlebotomy when Hb rose to 19.1 g/dL. Two months later, he developed right flank pain, and CECT revealed right renal vein thrombosis with IVC extension (Fig. 4). Anticoagulation was switched to enoxaparin followed by acenocoumarol titrated to INR 2–3.

Three months later, he presented again with chest pain and dyspnea; CTPA revealed left pulmonary artery thrombosis, managed with alteplase. Despite tacrolimus, steroids, and anticoagulation, proteinuria persisted (6 g/24h), and anti-PLA2R antibody increased (158 RU/ml). He was subsequently initiated on the Modified Ponticelli regimen at last follow-up.

DISCUSSION

Polycythemia classified as Primary polycythemia caused by erythropoietin (EPO) receptor mutations or Janus Kinase 2 (JAK2) mutations [1] & Secondary Polycythemia due to nephrotic syndrome is an unusual association & rarely reported. Most reported association is of FSGS with polycythemia vera [4–9]. Association of MCD and polycythemia has also been reported previously [10, 11]. Renal conditions which increases renal mass caus-

ing increased EPO production, are commonly associated with secondary polycythemia like kidney tumors, bilateral hydronephrosis, polycystic diseases, post kidney transplantation, renal artery stenosis, & Bartter syndrome, but association with nephrotic syndrome like membranous nephropathy has been described rarely [2, 12]. To the best of our literature search, 5 cases of membranous nephropathy associated with Secondary polycythemia with membranous has been reported [13-17]. Negative JAK2 mutation and normal serum erythropoietin excluded diagnosis of Polycythemia vera & diagnosis of secondary polycythemia was considered after bone marrow biopsy revealed mild erythroid hyperplasia. Renal biopsy revealed PLA2R positive membranous nephropathy & blood investigations showed no evidence any cause of secondary membranous nephropathy.

The pathogenesis of polycythemia in membranous nephropathy remains speculative, with several mechanisms proposed. One explanation is the renal hypoxia hypothesis, where severe nephrosis and interstitial edema impair renal oxygen delivery, thereby stimulating erythropoietin (EPO) release via hypoxia-inducible pathways [14, 15]. Alternatively, a cytokine-mediated mechanism has been described, wherein glomerular injury induces pro-inflammatory cytokines such as interleukin-8, which can enhance erythropoiesis independent of hypoxia [2]. More recently, experimental studies suggest a potential podocyte-EPO axis, whereby podocyte injury alters paracrine signaling and tubular-interstitial crosstalk, modulating EPO production even in the absence of hypoxemia [17-19]. These mechanisms may act synergistically, and their relative contribution likely varies between patients, explaining the heterogeneity of reported cases.

Therapeutic phlebotomy has to be done along with long term anticoagulant which reduces the hyperviscosity & risk of thromboembolism, as was done in our patient along with rituximab. However, i/v/o persistent proteinuria & polycythemia with raised anti-PLA2R antibody on follow up, Modified Ponticelli

regimen was started.

In conclusion, association of polycythemia with Nephrotic syndrome is rare with FSGS being the most commonly reported with polycythemia vera. We here report a unique case of secondary polycythemia due to PLA2R positive membranous nephropathy causing recurrent venous thrombosis. Prompt clinical suspicion leading to early diagnosis and treatment with prednisolone, rituximab, calcineurin inhibitor along with angiotensin receptor blocker, anti coagulant can help control proteinuria and polycythemia, thereby reducing thrombosis risk. In the context of kidney transplantation, early identification and aggressive management of such complications may help optimize patient outcomes by reducing thrombotic risk, improving graft survival, and guiding individualized immunosuppressive strategies. This report also underscores the need for close hematologic and nephrologic monitoring in transplant recipients with nephrotic-range proteinuria, as timely intervention with combined anticoagulation and immunomodulatory therapy may prevent severe vascular events and preserve allograft function.

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CONFLICTS OF INTEREST: None declared.

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