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Case Report

# Anti PLA2R Ab-Positive Membranous Nephropathy in a Patient with Eosinophilic Variant Chromophobe Renal Cell Carcinoma: A Case Report

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## ABSTRACT

Membranous Nephropathy (MN) is the most common cause of nephrotic syndrome in non-diabetic adults. It is characterized by the accumulation of immune complex deposits on the sub-epithelial side of the glomerular basement membrane. Malignancies, various infections, use of certain medications and autoimmune diseases have been described to be the common causes of secondary MN. Primary membranous nephropathy is characterized by the formation of circulating anti phospholipase A receptor 2 antibodies (AntiPLA2R Ab). We describe a rare case of a 37-year-old male of African descent who presented with nephrotic syndrome and found to have circulating AntiPLA2RAb as well as an eosinophilic variant of chromophobe renal cell carcinoma on the contralateral kidney. A partial nephrectomy and adjunctive supportive anti-proteinuric measures did not improve nephrotic syndrome. Partial remission of nephrotic syndrome was achieved after treatment with a combination of corticosteroids and oral cyclophosphamide in line with treatment of moderate and high-risk group patients with primary membranous nephropathy. This case is novel as it describes a patient with two disease processes that are not known to be related, yet both known to cause membranous nephropathy. The limited availability of AntiPLA2RAb testing at the treatment center resulted in a delay in establishing the diagnosis of primary membranous nephropathy. Unavailability of PLA2R antibody histology stains made it difficult to conclusively decide the causal effect of the circulating AntiPLA2R antibodies in this patient. Concerted efforts to improve cost-effective availability of antiPLA2R antibody testing in South African public sector are needed. Laparoscopic partial nephrectomy was uneventful, and it precluded nephron loss and preserved glomerular filtration rate in this patient.

## INTRODUCTION

Membranous nephropathy accounts for an estimation of 20-30% of cases of nephrotic syndrome in adults [1]. It is characterized by the accumulation immune complex deposits on the sub-epithelial side of the glomerular basement membrane. Membranous nephropathy (MN) is seen in all ethnic and racial groups and both sexes, however, primary membranous nephropathy is more common in white males that are above the age of 40 years. Primary membranous is characterized by the formation of circulating anti phospholipase A receptor 2 antibodies (AntiPLAR2Ab) which can be detected on the biopsies and test positive in the serum of about 70% of cases.

Seropositivity with anti -thrombospondin type-1 domain-containing 7A(THSD7A) has been described in some patients with primary membranous nephropathy, however, the availability of this test in most clinical settings remains limited. Malignancies, various infections, use of certain medications and autoimmune diseases have been described to be the common causes of secondary MN. Serum positivity for AntiPLAR2Ab and positive staining for antiPLAR2 Ab on the tissue with predominant immunoglobulin G (IgG) granular pattern is seen in MN with subclass IgG4 in primary MN and non-IgG-4 sub-class is prevalent in secondary MN [2]. Mesangial deposits and immunofluorescence positivity with C1q also suggests secondary MN [3]. Although primary and secondary MN are distinct entities, they tend to share similar clinical and pathological course.

Up to 20% of cases with secondary membranous nephropathy have a malignancy, particularly if they are above the age of 65 years of age. The MN may precede the malignancy or it may occur at the same time or post remission. MN is commonly associated with solid tumors such as prostate, lung and breast tumors as well as hematological malignancies such as chronic lymphocytic leukemia [4]. Paraneoplastic glomerulopathy associated with renal cell carcinoma (RCC)was initially overlooked but review of cases show that 10-40% of patients with RCC have paraneoplastic phenomena with some that show features of paraneoplastic glomerulopathy. In the review by Tojo et al., the patients had IgA, FSGS or diabetic nephrosclerosis.

The 2016 WHO classification for renal cell carcinoma classify tumors according to cytoplasmic features, architectural features, anatomical location of tumor, correlation with a renal disease background, familial predisposition syndromes or molecular alterations pathognomic for RCC subtypes. Chromophobe RCC is classified under the group of RCC with certain cytoplasmic features. The classic description is that of 'plant cell appearance' with pale cytoplasm and a perinuclear halo on electron microscopy and typically stain positive for Hale colloidal iron. Thirty percent consist of an eosinophilic variant that can have features like an oncocytoma (Moch et al.) [5].

Chromophobe RCC are commonly sporadic tumors that are characteristically well circumscribed tumors and are rare, accounting for approximately 5-7% of all RCCs [6]. They are thought to show differentiation towards intercalated cells of the distal tubule. The sporadic form can be associated with a mutation that results in downregulation of pP53 tumor suppressor signaling whereas non-sporadic forms can be seen in the context of Birt-Hogg-Dube' syndrome, an autosomal dominant disorder associated with mutation in the Folliculin gene and Cowden syndrome which results from the mutations in the PTEN [7]. Eosinophilic variant of chromophobe RCC predominantly consists of eosinophilic cells and they can be easily be mistaken for oncocytomas. They carry similar prognostic outcomes to classic chromophobe RCC. Chromophobe RCC has been shown to carry a better prognosis compared to clear cell RCC and papillary RCC. Most chromophobe RCC has a low metastatic risk with a predilection for the the liver when it does metastasize [8].

## CASE REPORT

We present a case of a 37–year-old man of African descent who was referred to a tertiary nephrology unit a year after he had been managed at a district hospital level with complaints of lower leg oedema and a new diagnosis of hypertension. He was not known to have any chronic illnesses and had not been taking any over-the-counter, prescribed or recreational drugs prior to the onset of his symptoms.

The patient was of normal build, with pitting oedema up to the knees and leukonychia. No vasculitic skin lesions nor skin rashes were noted. He was hypertensive (Blood pressure: 150/100 mmHg) with a pulse rate of 92 beats/min. His abdominal examination showed abdominal wall edema and features in keeping with ascites. His cardiovascular, respiratory and neurological were further unremarkable.

Urinalysis revealed proteinuria +3, blood 1+ with bland urine sediment. Twenty-four hours' urine protein excretion was 11.4 g/24 hrs. of protein, serum albumin was 9 g/dL and serum cholesterol was 10.09 mmol/L. Serum creatinine was 71umol/L with an estimated glomerular filtration rate of >60 mL/min/1.73m$^2$ by MDRD equation. Serum electrolytes revealed hypokalemia of 2.5 mmol/L and the rest of the electrolytes were normal. Full blood count, liver enzymes, thyroid function test and HbA1c were all within normal limits. HIV test was negative, hepatitis B surface antigen was negative and hepatitis C antibodies were also negative. RPR and TPHA

were also negative. Complement (C'3 and C'4) was within normal limits, antinuclear and extractable nuclear antibodies were negative. Serum protein electrophoresis and serum free light chain ratio were within normal limits. At the time that the patient presented, AntiPLA2Rantibody test was not performed as it is not offered by the laboratory providing services to public patients.

A kidney biopsy was planned and during pre-biopsy ultrasonography of the kidneys, a mass was suspected on the left kidney. A decision to proceed and biopsy the normally appearing right kidney was made.

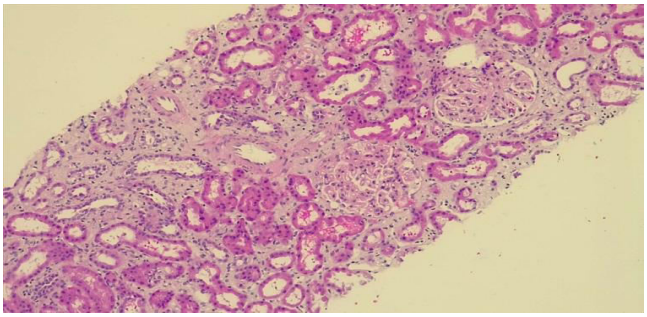

Figure 1: Light microscopy showing renal cortex with vascular changes of hypertension and a glomerulus with thick rigid glomerular loops.

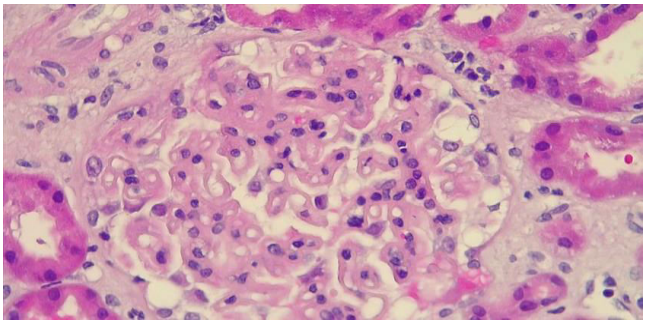

Figure 2: Light microscopy showing a closer view of the thickened glomerular loops

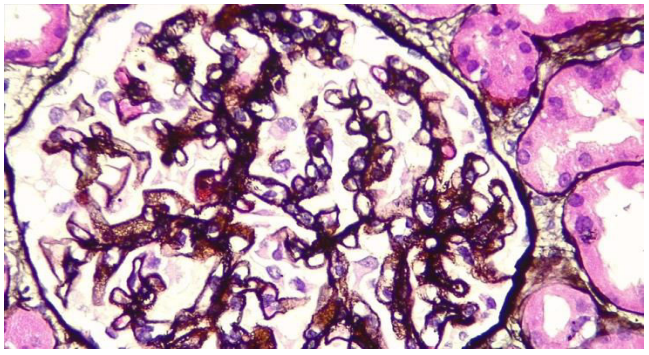

Figure 3: light microscopy with silver stain showing the moth-eaten appearance, a typical finding in membranous nephropathy.

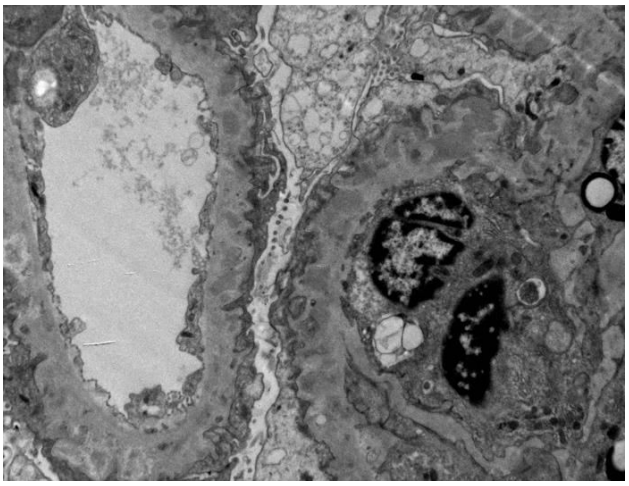

Figure 4: Electron microscopy findings showing intramembranous immune complex deposition in keeping with membranous nephropathy.

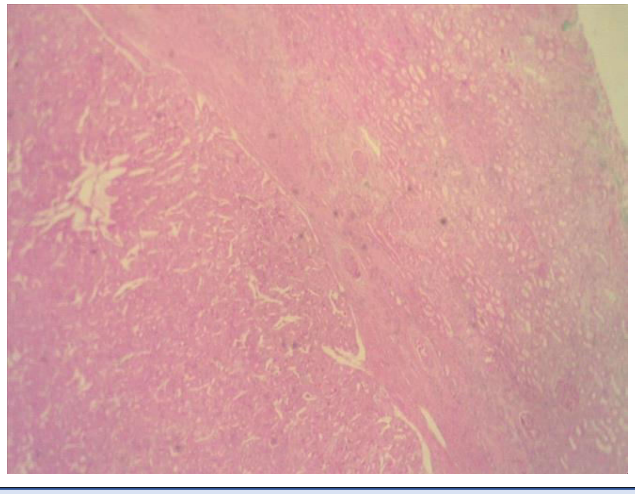

Figure 5: Light microscopy overview of kidney and adjacent tumour.

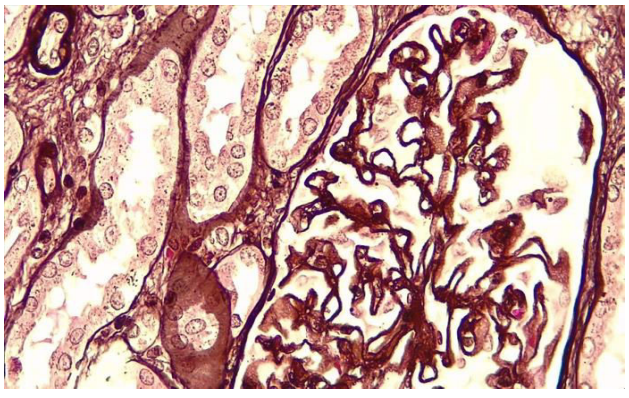

Figure 6: Membranous changes in kidney tissue adjacent to the tumour.



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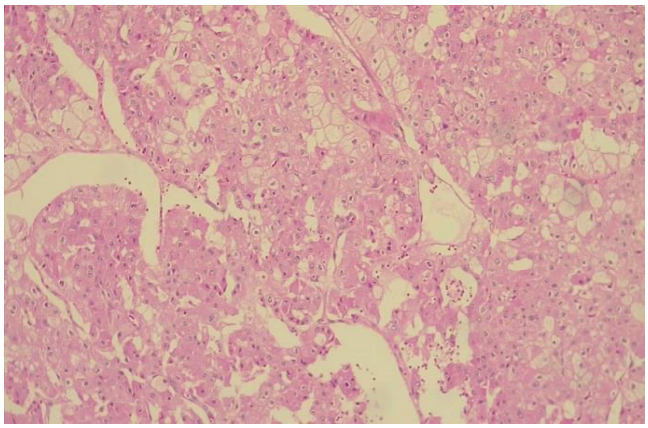

Figure 7: Light microscopy showing eosinophilic tumour cells in nests.

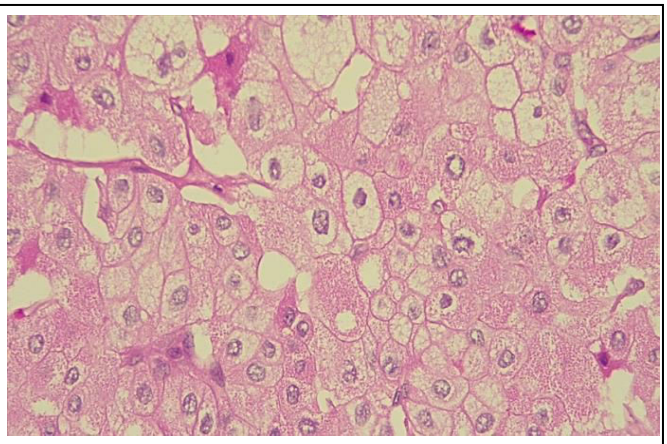

Figure 8: Prominent cell membranes, granular cytoplasm and raisinoid nuclei.

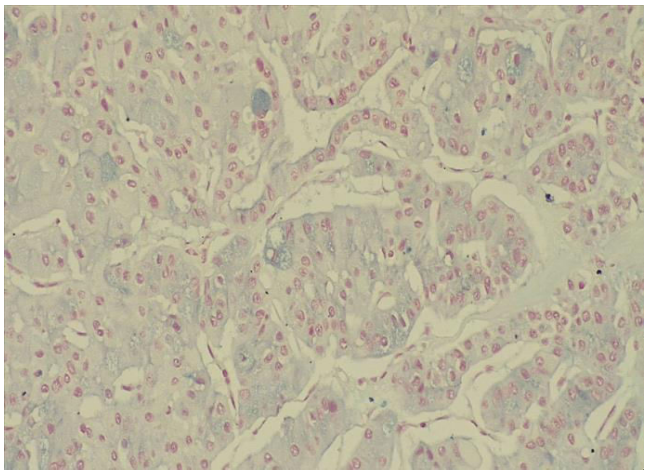

Figure 9: Hale's colloidal iron staining blue in the cytoplasm.

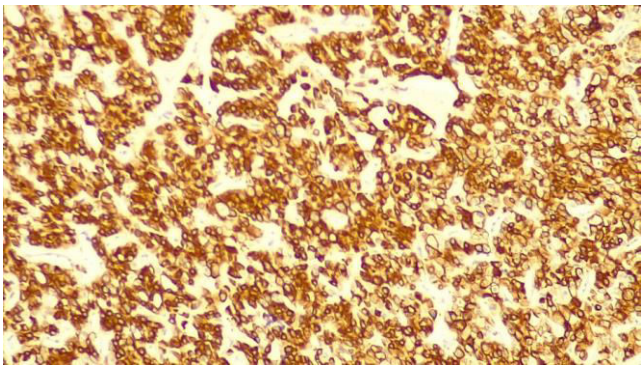

Figure 10: CK 7 strongly diffuse positivity.

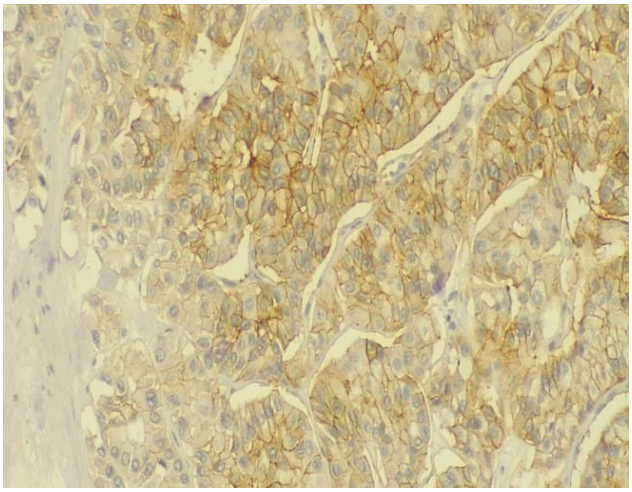

Figure 11: CD117 membranous staining.

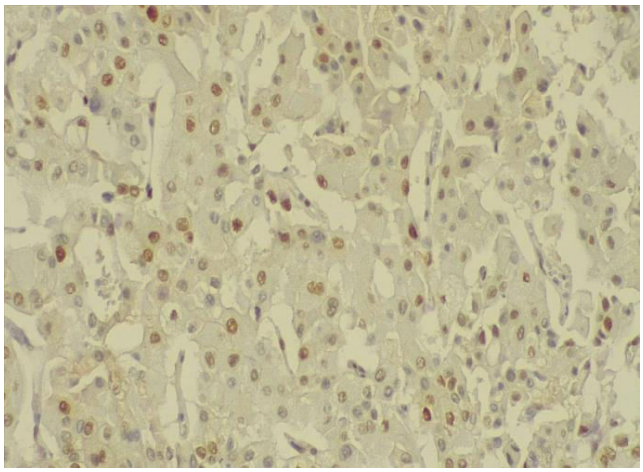

Figure 12: Cyclin D1 nuclear dot positivity.



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The histological findings are shown in Figures 1-4, which reveals typical findings of membranous glomerulopathy. Light and electron microscopy are not able to distinguish between primary and secondary membranous glomerulopathy with certainty. In the kidney biopsy, 20 glomeruli were present with two showing age-related global sclerosis. The remaining glomeruli had thick rigid glomerular basement membranes. The silver stain showed focal spike formation, but most areas had a moth-eaten appearance. The blood vessels showed early hyaline arteriolosclerosis and myointimal hypertrophy and hyperplasia associated with benign hypertension. No significant interstitial fibrosis or tubular atrophy was noted. Immunofluorescence performed with IgA, IgM, IgG, C3, C4 and C1q showed focal sub-epithelial dots with IgG, IgM and C4. The rest of the immunofluorescence stains were negative. Electron microscopy performed on the tissue received in glutaraldehyde showed numerous sub-epithelial immune complex deposits with extension of the basement membrane around the complexes. Some of the complexes were starting to dissolve. There was extensive foot process effacement of the overlying podocytes. These findings are consistent with stage III membranous glomerulopathy.

A computed tomography (CT) examination of the abdomen was performed to further evaluate the possible left renal mass. CT showed a 5cm x 5cm contrasting enhancing mass on the anterior lower pole of the left kidney without associated lymphadenopathy, renal vein thrombosis or evidence of distant metastasis. Radiological features were in keeping with a renal cell carcinoma. CT urography excretory phase demonstrated the mass abutting lower pole renal calyx and upward displacement of renal pelvis. Renal nephrometry score were calculated as 9a (intermediate complexity).

A laparoscopic partial nephrectomy was performed. Port placement included a 10 mm camera port, 12 mm instrument port, 5 mm instrument port and another 5 mm port for assistant with suction. The descending colon was mobilized, the renal artery and vein isolated, and the lower pole tumour exposed by opening overlying Gerota's fascia. Tumor was noted in close proximity to renal pelvis and ureter. The renal artery was clamped, and the tumour enucleated without entering renal collecting system. Renal parenchyma was approximated with 33-minutes warm ischaemia time and estimated blood loss of 50 mL. There were no post-operative complications.

**Histological findings of the partial nephrectomy specimen:**

Gross examination of the partial nephrectomy showed two specimens. The first specimen was identified to be a partial nephrectomy that weighed 58.8 g and measured 55 x 45 x 45 mm. A multinodular lesion was present, and it appeared to be shelled out and surrounded by a fibrous pseudo-capsule. The lesion was homogenous tan in appearance with areas of hemorrhage and central necrosis. The second fragment consisted of fibro-fatty tissue and two lymph nodes were present.

Light microscopy of the tumour in the kidney showed nests of tumour cells consisting of large pleomorphic cells with well-defined cell borders and granular eosinophilic cytoplasm. Raisinoid nuclei surrounded by a clear halo could be identified. The tumor breached the fibrous pseudo-capsule in some areas. A Hale's colloidal iron stain was positive. Immunohistochemically stains for CK7, CD117 and cyclin D1 were positive. The following stains were negative: CK20, S100, Dog1, vimentin. The morphology together with the variable IHC findings were most consistent with an eosinophilic variant of chromophobe renal cell carcinoma (11 and 12). No tumour could be identified in the lymph nodes. In the adjacent kidney, similar membranous glomerulopathy changes were present as was seen in the original kidney biopsy.

## MANAGEMENT OF THE PATIENT AND OUTCOME

At the time of presentation, the patient had been on maximum tolerated dose of angiotensin-converting-enzyme inhibitor for more than a year without improvement of proteinuria. The antiproteinuria treatment, diuretics and other supportive measures were continued for 3 months beyond the nephrectomy with marginal improvement of serum albumin and no improvement of the albuminuria. A decision to explore a possibility of primary membranous nephropathy was taken and AntiPLA2R antibody test was done through a private laboratory which was funded by the principal investigator. The AntiPLA2R antibody test was positive with a titre of 1:160 and a decision to initiate modified Ponticelli regimen as recommended by KDIGO guidelines was taken as the extent of the edema had impaired the mobility of the patient by this

stage, an indication for immunosuppression treatment. The modified Ponticelli regimen consists of cyclical pulses of methylprednisone over three days followed by oral prednisone and oral cyclophosphamide on alternative months. Over a 6-month period of receiving immunosuppression treatment, the patient achieved partial remission with complete resolution of his edema and remarkable improvement of his blood pressure control. Table 1 summarizes the biochemical findings of the patient.

Table 1: Biochemical profile displaying partial remission after initiating immunosuppression treatment.

| | At Presentation On Maximum tolerated ACEi Dose(>12 months) | 2 Months Post-Nephrectomy (Initiated Modified Ponticelli regimen at this point) | 4 months Post Nephrectomy & Initiation of Immunosuppression | Immunosuppression and ACEi Month 2 | Immunosuppression and ACEi Month 4 |
|---|---|---|---|---|---|
| Urine protein creatinine ratio g/mmol creatinine | 0.114 | 0.116 | 0.120 | 0.0107 | 0.058 |
| Serum Albumin g/dL | 9 | 11 | 14 | 27 | 32 |
| EGFR by MDRD equation (mL/min/ 1.73m$^2$) | >60 | >60 | >60 | >60 | >60 |
| Phospholipase A2 Receptor Ab | | Positive Titer: 1:160 | Not Done | Not Done | Not Done |

## DISCUSSION

Glomerular disease can be paraneoplastic manifestations of various malignancies, including hematological and solid organ malignancies. Cancer-associated membranous nephropathy is one of the common glomerular diseases encountered by onco-nephrologists. A few cases of RCC and membranous glomerulopathy were identified via a PubMed search, however, none of them were associated with positive anti PLA2R ab serology [9,10].

The outcomes of cancer associated MN are heterogeneous and this is most likely due to the complexity of the underlying pathogenesis that differs with various forms of malignancies. However, most patients display improvement of proteinuria after resection of the tumor where possible, or after achieving remission.

Membranous nephropathy is among the most common causes of nephrotic syndrome in non-diabetic adult patients [9]. The prevalence of membranous nephropathy as the cause of nephrotic syndrome is estimated to account for about 2015 of cases. A study that described the patterns of kidney diseases in Cape Town in 2011, found the prevalence of membranous nephropathy to be 18.5% over the 10-year period [10]. Most of the patients were predominantly black although literature describes this disease to affect mostly males who are Caucasians and above the age of 40 years. The discovery of AntiPLA2R as a target antigen in most patients with what was previously believed to be idiopathic, now called primary membranous nephropathy, advanced the knowledge of understanding the pathophysiology and devising novel therapeutic strategies for this disease. Primary membranous nephropathy accounts for about 80% of all cases and the remaining 20% is secondary to various underlying diseases such as malignancies, infections, autoimmune disorders, and exposure to certain drugs. The management of secondary membranous nephropathy entails treating the cause or withdrawing the offending drug in cases of drug induced membranous nephropathy.

The discovery of the anti-PLA2R ab serology testing has caused a paradigm shift in the management and monitoring of patients with membranous nephropathy. There have been major strides made in advancing the studying of patients with primary membranous nephropathy and this has led to the discovery of more therapeutic options that have a better safety profile than the alkylating agents [11]. As with many autoimmune diseases, the triggering event of developing these circulating antibodies is unknown. Most models suggest genetic predisposition and environmental factors as a second hit that is required to get the disease process going.

Due to the limited availability of AntiPLA2R ab testing in the public sector, the prevalence of primary membranous nephropathy in South Africa is unknown. Without a diagnosis of

primary membranous nephropathy, appropriate management is impossible, which increases risk of progression of kidney disease and poor outcomes. This needs to be addressed to align the management of these patients to international guidelines and standards. This is especially important in the South African context, where access to kidney replacement therapy is limited due to resource constraints. Thus, more robust efforts should be made to improve availability of preventive, diagnostic and therapeutic tools that will halt or delay progression of kidney diseases in the public sector.

This case demonstrates a rare case where two disease processes that are known to cause membranous nephropathy coexisted and managing the renal cell carcinoma with laparoscopic partial nephrectomy did not result in any improvement of the nephrotic syndrome. Deeper search for alternative explanation for poor response after partial nephrectomy led to the discovery of the presence of circulating antiPLA2R antibodies. The quick response to immunosuppression made us believe that the circulating antiPLA2R antibodies had a causal effect, although a PLA2R antibody histology stain would have added more value to confirm the diagnosis. It is unknown whether the immune response targeted to the cancer in this patient, could have contributed to the development of the AntiPLA2R antibodies or incited relapse or progression of a quiescent disease.

We were delighted that the patient tolerated the alternating months of receiving oral cyclophosphamide and corticosteroids with no side effects, as this is often the limitation of this regimen and in our setting, alternative options such as rituximab are not readily available.

## CONCLUSION

Membranous nephropathy is the most common glomerular disease associated with malignancies. In South Africa, robust efforts are needed to improve the availability of AntiPLA2R antibody serology testing to optimize diagnostic and therapeutic options in patients with primary membranous nephropathy in the public healthcare sector. Laparoscopic partial nephrectomy is associated with few perioperative complications, better nephron and GFR preservation.

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