Kidney Medicine

Secondary Membranous Nephropathy Due to Benign Tumors in 2 Young Women: A Case Report

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Membranous nephropathy (MN) is one of the most common causes of adult-onset nephrotic syndrome. We describe the cases of 2 young women in their 20s presenting with nephrotic syndrome due to antiphospholipase A_2 receptor (anti-PLA_2R)–negative MN, that was found to be associated with benign tumors. Both women had no extrarenal symptoms of a connective tissue disease, infection, or malignancy. They both had been previously healthy and were not receiving treatment with any drugs. Both had MN on kidney biopsy. Biopsies were negative for PLA_2R antigen, and their serum did not demonstrate the presence of anti-PLA_2R antibodies. Both were investigated for a secondary cause on the basis of negative anti-PLA_2R serology and biopsy features supportive of secondary MN and were found to have benign tumors on radioimaging: a uterine leiomyoma and mesenteric fibromatosis, respectively. In both instances, the nephrotic syndrome remitted following resection of the tumors. To our knowledge, uterine leiomyoma and mesenteric fibromatosis have not previously been described in association with MN. These cases highlight the importance of pursuing a secondary cause of MN in patients without anti-PLA_2R antibodies in serum or PLA_2R antigen on kidney biopsy.

Complete author and article information provided before references.

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INTRODUCTION

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome among adults. It accounts for approximately 25% of all cases with a peak incidence around the fourth to fifth decade of life.[1] Approximately 80% of cases are primary membranous and 20% are secondary to systemic disease or exposures. Podocyte M-type antiphospholipase A_2 receptor (anti-PLA_2R) is now known to be the target antigen in the majority of primary or "idiopathic" MN cases, and anti-PLA_2R antibodies play a useful role in diagnosing primary MN, with a sensitivity of 70%-80%.[2,3]

Fifteen percent of patients with MN, who do not have detectable anti-PLA_2R antibodies in serum, have PLA_2R antigen staining on kidney biopsy as demonstrated by immunohistochemistry microscopy.[4] Other antigens that have been linked to primary MN include thrombospondin type 2 domain-containing 7A, to which antibodies are found in 3%-5% of primary MN cases,[5,6] and the recently identified neural tissue-encoding protein with epidermal growth factor–like repeats (NELL1), which may be associated with up to 16% of cases.[7] Exostosin 1 and 2 have been identified to be associated with secondary MN in autoimmune disease.[8]

The absence of detectable anti-PLA_2R antibodies in serum and PLA_2R staining on kidney biopsy, although not diagnostic, is suggestive of a secondary cause for MN and supported by other clues such as positive immunohistochemistry for IgG1, IgG2, IgG3, IgM, IgA, C3, and C1q (vs IgG4 and C3 in primary membranous disease) and the presence of subendothelial and mesangial deposits (vs subepithelial in primary disease) or tubular reticular inclusions (absent in primary disease) on electron microscopy.[1]

Secondary causes of MN are broadly categorized as infections, neoplasia, drugs, and connective tissue diseases. The likely etiology varies according to age, sex, and geographic location. For example, systemic lupus erythematosus is a common cause among young females, malignancy in elderly individuals, and chronic hepatitis B in Eastern Asia.[1,9] In a cohort of 240 White patients with MN, 24 had malignancy at the time of biopsy or within 1 year. The risk of associated malignancy increased with age and was 1 in 4 over the age of 65 years and 1 in 50 among those under the age of 55 years.[10] Common malignancies associated with MN include lung, breast, colon, and prostate cancer. Antibodies to thrombospondin type 2 domain-containing 7A have been identified in association with gall bladder carcinoma, in which malignant gall bladder tissue also tested positive for thrombospondin type 2 domain-containing 7A antigen, suggesting that these play a role in secondary MN as well.[11]

We present the cases of 2 young women with anti-PLA_2R antibody–negative MN that occurred in association with benign neoplasms and resolved following surgical resection. The timeline for each case is presented in Box 1. These cases highlight the need to investigate the underlying cause of MN even in young patients if they test negative for anti-PLA_2R antibodies.

CASE REPORT

Case 1

A woman in her mid-20s presented with new-onset generalized body swelling. She had no features of multisystemic disease, was not receiving treatment with any medications, and had no high-risk behavior. She was

Box 1. Patient Timelines

Case 1

Time 0	• Patient presents with generalized edema of new onset • Nephrotic syndrome is confirmed (urine protein-creatinine ratio, 650 mg/mmol) • Undergoes kidney biopsy; diagnosed as membranous nephropathy, some features suggest a secondary cause • Antiphospholipase A_2 receptor antibodies are absent in serum • Virology and automimmune panel is negative
1.5 months	• A computed tomography scan of abdomen shows heterogeneous mass within the right pelvis, measuring up to 14 cm, which appeared to be arising from the right adnexa; the heterogeneous appearance is suspicious for sarcomatous change
2 months	• Surgical resection of the mass • Histology shows a uterine leiomyoma • Preoperative proteinuria was 267 mg/mmol
3 months	• Proteinuria reduces to 1 g/24 h
5 months	• Proteinuria is 0.35 mg/mmol • Remission achieved

Case 2

Time 0	• Patient presents with generalized edema of 7 weeks; nephrotic syndrome is confirmed (urine protein-creatinine ratio, 888 mg/mmol)
2 weeks	• Undergoes kidney biopsy; diagnosed as membranous nephropathy, some features suggest a secondary cause • Antiphospholipase A_2 receptor antibodies are absent in serum • Virology and automimmune panel is negative
1 month	• Treatment with prednisolone and mycophenolate mofetil is started as for seronegative lupus • Supportive treatment for nephrotic syndrome continued
4 months	• A computed tomography scan of the abdomen shows small, slightly spiculated soft tissue nodule measuring 3.1 cm within the ileocolic fat suspicious for a neuroendocrine tumor • Immunosuppression weaned and stopped
6 months	• Patient undergoes a hemicolectomy. Histopathology of the resected sample shows a mesenteric mass consisting of sweeping fascicles of bland spindle cells infiltrating into the surrounding fat with patchy staining for β-catenin • At the time of surgery, proteinuria is 388 mg/mmol
9 months	• Proteinuria reduces to 9 mg/mmol
18 months	• Proteinuria is 4 mg/mmol • Complete remission achieved

otherwise healthy, with no previous medical history. Her systemic review was unremarkable. She had no family history of kidney disease. On examination, she had a generalized edema. Findings of skin, oral mucosa, and joint examination was normal. Blood pressure was 120/82 mm Hg. Urine dipstick test results were positive for protein (4+) and negative for blood. She had nephrotic syndrome, as demonstrated by a urine protein-creatinine ratio of 605 mg/mmol and a serum albumin level of 26 g/dL. Serum creatinine level was 35 μmol/L, and cholesterol level was 11.5 mmol/L. Her antinuclear antibody and anti–double-stranded DNA antibody test results and viral screening for hepatitis B virus, hepatitis C virus, and HIV (human immunodeficiency virus) were negative, and her complement levels were within the normal range. Anti-PLA_2R antibody serology was negative.

She proceeded to a kidney biopsy that sampled 21 glomeruli (Fig 1A-G). The glomeruli were almost normal on light microscopy, which only showed occasional irregularities of the capillary walls but no spikes or duplications and no proliferative changes. Immunostaining showed subtle, pseudolinear positivity for IgG, IgA, IgM, C1q, and C3. Electron microscopy revealed occasional small discrete subepithelial deposits but no subendothelial or mesangial deposits and no tubuloreticular inclusions. In combination with the electron micrographs, immunostaining was interpreted as finely granular staining of capillary walls that was distributed diffusely and globally with background mesangial staining for IgM and C1q, in keeping with early membranous disease. The glomerular basement membranes were of normal thickness, and there was widespread podocyte foot process effacement on electron microscopy. The kidney tissue stained negative for PLA_2R antigen. The collective findings were suggestive of a secondary MN.

She received supportive management with an angiotensin-converting enzyme inhibitor, a statin, and furosemide. To identify the secondary cause, she underwent an ultrasound examination of the abdomen; the ultrasound scan demonstrated a pelvic mass. Subsequently, a computed tomography scan of her abdomen was obtained for further characterization. Her computed tomography scan showed a heterogeneous mass within

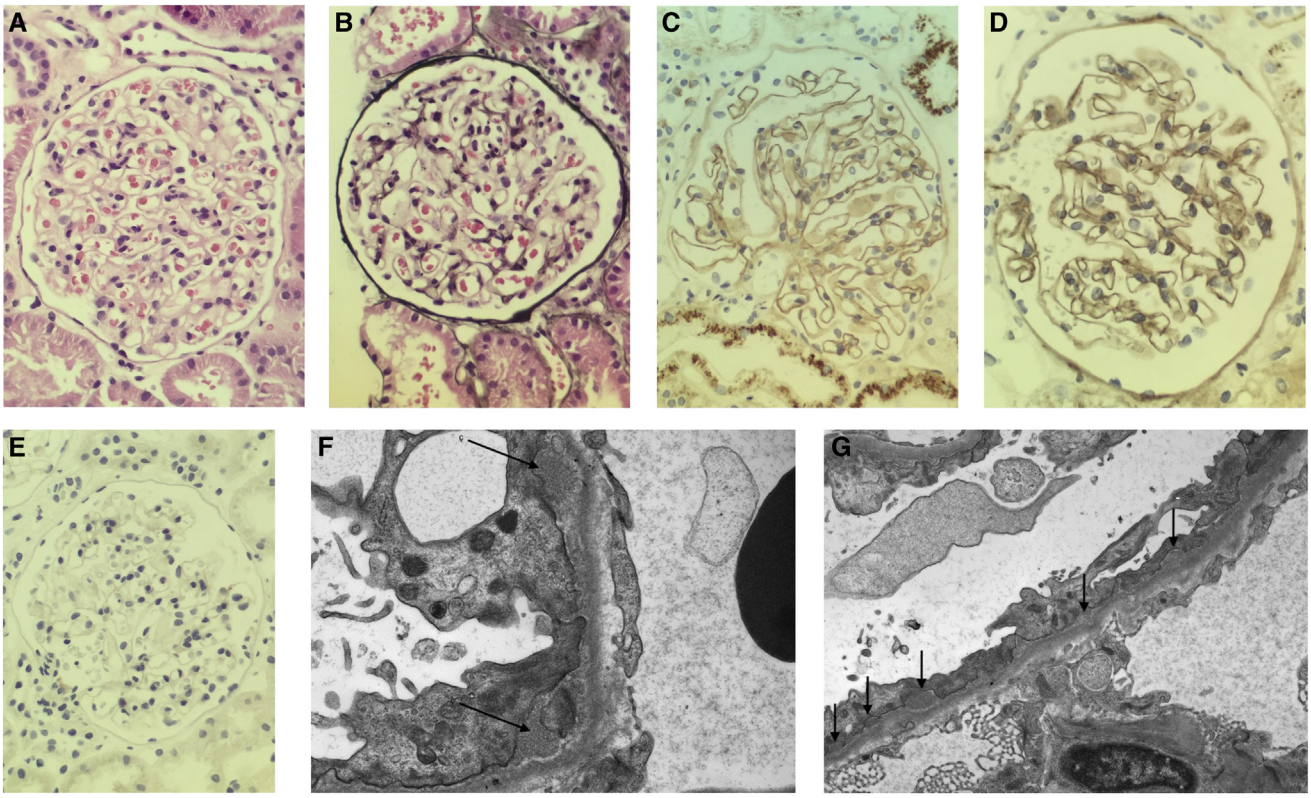

Figure 1. Kidney histology of case 1. (A) Hematoxylin and eosin staining (original magnification, ×40) and (B) periodic acid methenamine silver staining (original magnification, ×40) both show no visible abnormalities. Notably, capillary walls do not appear thickened on hematoxylin and eosin staining, and no spikes are visible on periodic acid methenamine silver staining. (C) Phospholipase A_2 receptor staining (original magnification, ×40) was negative. (D) Immunohistochemistry for IgG (original magnification, ×40). (E) Immunohistochemistry for C3 (original magnification, ×40). IgG and C3 immunostains show subtle, pseudolinear positivity. In combination with the electron micrographs, this was interpreted as finely granular positivity, in keeping with early membranous glomerulopathy. (All immunostains for IgG, IgA, IgM, C1q, and C3 showed similar staining patterns.) (F) Electron microscopy images (original magnification, ×5000) and (G) (original magnification, ×2500) demonstrate subepithelial electron-dense deposits (arrows) with overlying podocyte foot process effacement.

the right pelvis, measuring up to 14 cm, which appeared to be arising from the right adnexa. The heterogeneous appearance was suspicious for sarcomatous change, and she proceeded to undergo a surgical resection of the mass 2 months after presentation. The histology of the resected specimen was suggestive of a uterine leiomyoma; the specimen, unexpectedly, stained positive for PLA_2R antigen (Fig 2).

Following surgery, she went into remission. Within 1 month after surgery, her protein excretion had decreased to 1 g/24 h; 3 months after surgery, her protein excretion was 0.35 g/24 h. Her protein excretion remained within the normal range 9 months following surgery. Table 1 demonstrates her blood results before and after surgical resection.

Case 2

A woman in her 20s of Caribbean ethnicity presented with ankle edema for 7 weeks. She had no fever, weight loss, or anorexia and no symptoms suggestive of a multisystemic disease. Her medical history was significant for well-controlled asthma managed with salbutamol inhalers. She had no history of high-risk behavior. She had no family history of kidney or autoimmune disease. On examination, she had edema up to her thighs. Blood pressure was 118/72 mm Hg. She had normal findings of skin and joint examination and had no lymphadenopathy. She had protein (4+) and trace blood on urine dipstick test. Her urine protein-creatinine ratio was 888 mg/mmol, serum creatinine level was 62 μmol/L, serum albumin level was 23 g/L, and total cholesterol level was 9.8 mmol/L, confirming nephrotic syndrome.

She tested negative for antinuclear antibody and anti–double-stranded DNA antibody and had no detectable paraprotein. Findings for hepatitis B virus, hepatitis C virus, and HIV antibodies were negative. Her anti-PLA_2R antibody test was negative. Kidney biopsy showed relatively normal glomeruli on light microscopy, suggestive of minimal change disease or early MN. Immunohistochemistry was negative for IgM, C3, and C1q. Electron microscopy demonstrated numerous mesangial and paramesangial electron-dense deposits as well as frequent

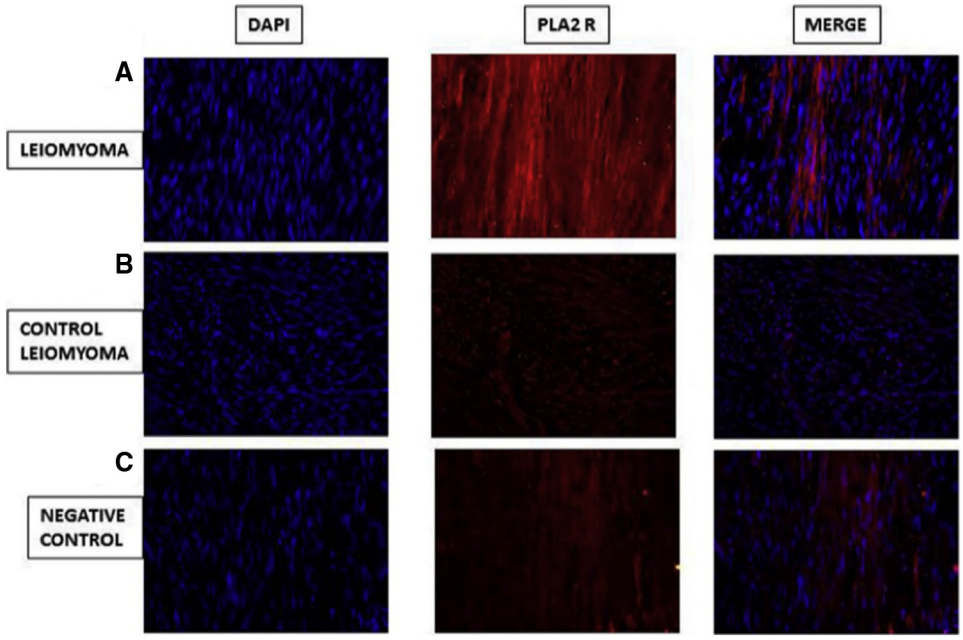

Figure 2. Phospholipase A_2 receptor (PLA_2R) expression in leiomyoma sections evaluated using immunofluorescence. (A) PLA_2R expression in case 1 with membranous glomerulonephritis compared with control leiomyoma (B). (C) When antibody against PLA_2R was omitted, no staining was present. Original magnification, ×400.

subepithelial electron-dense deposits, suggestive of secondary membranous disease. The kidney biopsy stained negative for PLA_2R antigen (Fig 3A-F).

Warfarin, an anticoagulant, was administered to the patient, and she started receiving treatment with losartan and a statin for supportive management. Because she was symptomatic with nephrotic syndrome with significant edema despite renin-angiotensin-aldosterone blockade, she started receiving treatment with prednisolone and mycophenolate mofetil for possible seronegative/lupus nephritis. Meanwhile, she was further investigated for a potential secondary cause.

A computed tomography scan of her abdomen was obtained; it showed a small slightly spiculated soft tissue nodule measuring 3.1 cm within the ileocolic fat, suspicious for a neuroendocrine tumor. Following detection of the mass, her immunosuppression was weaned and stopped, and she subsequently underwent a hemicolectomy. The histopathology of the resected sample showed a mesenteric mass consisting of sweeping fascicles of bland spindle cells infiltrating into the surrounding fat with patchy staining for β-catenin (Fig 4).

A diagnosis of mesenteric fibromatosis was made. Before surgery, her urine protein-creatinine ratio remained elevated at 338 mg/mmol with significant edema requiring diuretics in the context of serum albumin that had been improving over the preceding 6 months. Following her surgery, there was a rapid clinical improvement, along with a reduction in proteinuria and diuretic requirement for management of edema. Three months after surgery, her urine protein-creatinine ratio had improved to 79 mg/mmol, and serum albumin levels had improved to 38 g/L at 3 months and 41 g/L at 6 months following resection (Table 2).

Table 1. Blood Results of Case 1 Before and After Surgery

	Serum Albumin (g/L)	Urine Protein-Creatinine Ratio (mg/mmol)	Cholesterol (mmol/L)
At presentation	24	605	11.5
Before surgery	27	267	11.8
3 mo after surgery	NA	—[a]	NA
12 mo after surgery	49	8	NA
24 mo after surgery	48	Undetectable	4.6

Abbreviation: NA, not available.
[a]One month after surgery, protein excretion was 1 g/24 h, with excretion of 0.35 g/24 h by 3 months after surgery.

DISCUSSION

Most centers routinely screen patients with MN for autoimmune disease with antinuclear antibodies, complement levels, and anti–double-stranded DNA antibodies; and infections with hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibodies, and antibodies against HIV-1 and HIV-2 and with Venereal Disease Research Laboratory test. Depending on the geographic location, screening for infections such as malaria, schistosomiasis, leprosy, filariasis, or hydatid disease may be part of a routine work-up. KDIGO (Kidney Disease: Improving Global Outcomes) recommends screening for neoplasia in

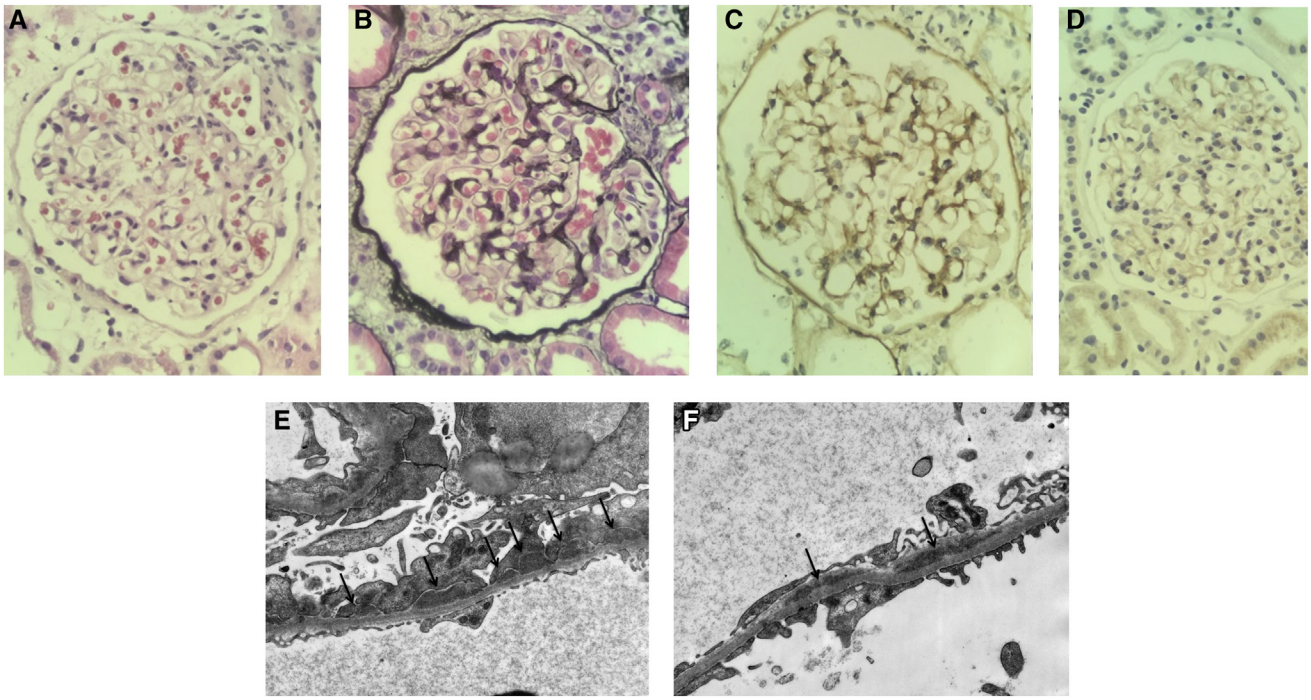

Figure 3. Kidney histology of case 2. (A) Hematoxylin and eosin staining (original magnification, ×40) and (B) periodic acid methenamine silver staining (original magnification, ×40) appeared normal. (C) Immunohistochemistry for IgG was negative (original magnification, ×40). (D) Phospholipase A_2 receptor staining was negative (original magnification, ×40). (E) Electron microscopy image (original magnification, ×2500) showed predominantly subepithelial deposits (arrows), indicating a membranous glomerulopathy. (F) Electron microscopy image (original magnification, ×2500) showed subendothelial electron-dense deposits (arrows). The small number of subendothelial and mesangial deposits suggests a secondary form of membranous nephropathy.

older patients; however, there is no consensus on the extent of work-up that is required, or for how long patients must continue to be screened, before neoplasia can be excluded as being causative.[9]

There is no such recommendation in younger patients who are generally considered less likely to have benign or malignant neoplasia. The guidance is likely to be confounded by the fact that before the availability of anti-PLA_2R antibody testing, many younger patients would have been characterized as having primary MN, with secondary causes having been reasonably excluded. Now that we can identify anti-PLA_2R antibody–negative MN, it may be that we need to begin investigating these patients for secondary causes more intensely. This will avoid unnecessary toxicity of treating such patients as for primary disease and allow for diagnosis and treatment of the underlying disorder.

The rarity of reports on benign tumors causing MN may be due to underdiagnosis. These 2 cases described young women who presented with anti-PLA_2R–negative MN, with negative lupus and infectious serology. Both were found to have benign tumors, and they achieved clinical remission following tumor resection.

To our knowledge, uterine leiomyomas have not been described as a cause of MN. This may be because they are fairly common, and many of these patients may have been characterized as having a previous history of or coexistent fibroids. In our literature review, we came across 2 cases of MN associated with a gastric leiomyoma. The first case, which occurred in association with a thymoma and myasthenia gravis, is likely to have been a primary MN as, in the absence of anti-PLA_2R antibody status, the biopsy stained positive only for IgG and complement; the disease recurred several years after removal of the leiomyoma but with no concurrent recurrence of the tumor.[12] The second patient who appeared to have had secondary MN went into remission following treatment of the tumor.[13] Similarly, we did not come across any reported cases of desmoid tumors being associated with nephrotic syndrome. Benign tumors that have rarely been reported to be associated with MN include schwannomas, angiomatous fibrous histiocytoma, and hepatic adenomas.[9,14] There have been reports of benign ovarian teratomas and dermoid cysts presenting as nephrotic syndrome in young girls and women[15,16] and of a Sertoli-Leydig ovarian tumor in a 6-year-old patient.[17] Neurofibromatosis is known to be associated with MN, and there have been reports of thrombospondin type 1 domain-containing 7A being detected in both the kidney tissue and neurofibromatosis tissue, suggesting a causative link.[18]

It is possible that our patients might have entered a spontaneous remission with future surveillance had they not undergone surgery. However, the rapid decrease in proteinuria and clinical improvement following surgery in both cases was striking and now, after approximately 2 years since surgery in both cases, they remain in remission.

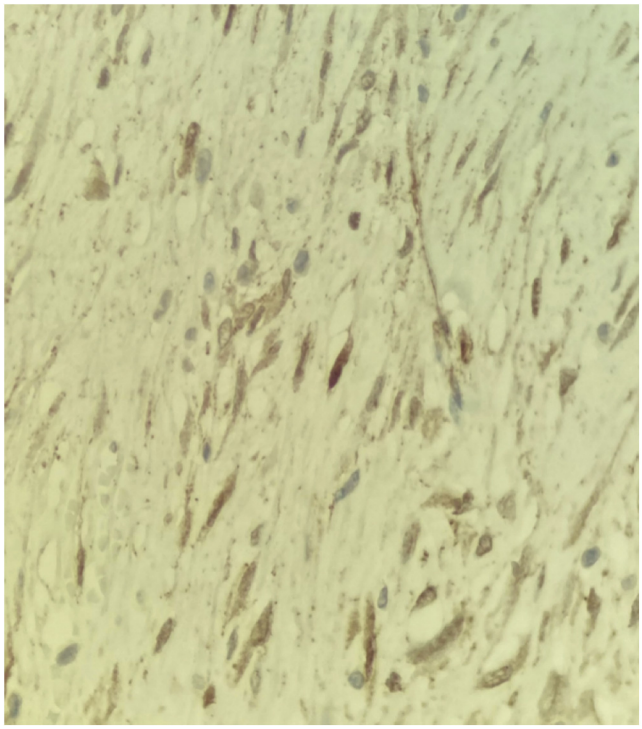

Figure 4. β-Catenin immunohistochemistry from the abdominal resection of the patient in case 2 shows nuclear positivity within the spindle cells of the mesenteric fibromatosis.

Further studies are necessary to determine the true molecular connection between certain benign tumors and secondary MN. For example, as discussed above, the association between the gall bladder carcinoma and MN via thrombospondin type 1 domain-containing 7A was identified when a patient with antithrombospondin type 1 domain-containing 7A antibody–positive MN was found to have a gall bladder carcinoma that stained positive for thrombospondin type 1 domain-containing 7A.[5]

One concern may be that benign asymptomatic tumors may be common, and increased detection of these may lead to unnecessary treatment of unrelated tumors without resolution of the nephrotic syndrome. We believe that, although this may be true, with our newer understanding of the pathogenesis of MN, we now need to develop a consensus on how intensively we should screen patients with anti-PLA_2R–negative MN for benign and malignant tumors. Further studies to identify molecular links between these tumors and MN may subsequently help us determine the ones that are likely to be clinically significant.

The availability of anti-PLA_2R antibody testing has changed our approach to the diagnosis of primary and secondary MN. We suggest that it is important to actively investigate the secondary causes of MN even in younger patients who screen negative for anti-PLA_2R antibodies in serum and antigen in kidney tissue. Benign tumors may be more common than we realize, and the identification of such tumors can lead to resolution of symptoms and avoid toxicity of unnecessary immunosuppression.

Table 2. Blood Results of Case 2 Before and After Surgery

	Serum Albumin (g/L)	Urine Protein-Creatinine Ratio (mg/mmol)	Cholesterol (mmol/L)
At presentation	23	888	9.8
Before surgery	36	338	5.6
3 mo after surgery[a]	38	79	4.7
12 mo after surgery	41	4	4.5

[a]One month after surgery, urine protein-creatinine ratio was 93 mg/mmol.

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REFERENCES

1. Yu A, Chertow G, Luyckx V. *Brenner and Rector's The Kidney*. 11th ed. Elsevier; 2019.
2. Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med*. 2009;361(1):11-21.
3. Bobart SA, De Vriese AS, Pawar AS, et al. Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. *Kidney Int*. 2019;95(2):429-438. doi:10.1016/j.kint.2018.10.021
4. Debiec H, Ronco P. PLA2R autoantibodies and PLA2R glomerular deposits in membranous nephropathy. *N Engl J Med*. 2011;364(7):689-690.

5. Tomas NM, Beck LH, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. *N Engl J Med*. 2014;371(24):2277-2287.
6. Tomas NM, Hoxha E, Reinicke AT, et al. Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy. *J Clin Invest*. 2016;126(7):2519-2532.
7. Sethi S, Debiec H, Madden B, et al. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. *Kidney Int*. 2020;97(1):163-174.
8. Sethi S, Madden BJ, Debiec H, et al. Exostosin 1/exostosin 2-associated membranous nephropathy. *J Am Soc Nephrol*. 2019;30(6):1123-1136.
9. Cattran DC, Feehally J, Cook HT, et al. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int Suppl*. 2012;2(2):139-274. doi:10.1038/kisup.2012.9
10. Lefaucheur C, Stengel B, Nochy D, et al. Membranous nephropathy and cancer: epidemiologic evidence and determinants of high-risk cancer association. *Kidney Int*. 2006;70(8):1510-1517.
11. Hoxha E, Wiech T, Stahl PR, et al. A mechanism for cancer-associated membranous nephropathy. *N Engl J Med*. 2016;374(20):1995-1996.
12. Calviño J, Adeva M, Sobrido MJ. Membranous nephropathy, leiomyoma and autoimmune myasthenia: more than a coincidence? *Clin Kidney J*. 2012;5(6):562-565. doi:10.1093/ckj/sfs144
13. Cimic A, Pastan SO, Bijol V. Membranous nephropathy associated with gastrointestinal stromal tumour: a case report. *NDT Plus*. 2009;2(4):306-308. doi:10.1093/ndtplus/sfp028
14. Zhang Z, Gong T, Rennke HG, Hayashi R. Duodenal schwannoma as a rare association with membranous nephropathy: a case report. *Am J Kidney Dis*. 2019;73(2):278-280.
15. Beauvais P, Vaudour G, Boccon Gibod L, Levy M. Membranous nephropathy associated with ovarian tumour in a young girl: recovery after removal. *Eur J Pediatr*. 1989;148(7):624-625. doi:10.1007/BF00441515
16. Jeroudi A, Kadikoy H, Gaber L, et al. Profound nephrotic syndrome in a patient with ovarian teratoma. *Saudi J Kidney Dis Transpl*. 2013;24(4):777-782.
17. Chen A, Vander Lugt M, McAllister-Lucas LM, Killen PD, Blatt NB. An unusual case of membranous nephropathy associated with an ovarian tumor. *Pediatr Nephrol*. 2011;26(12):2249-2251. doi:10.1007/s00467-011-1994-7
18. Lin F, Zhang D, Chang J, et al. THSD7A-associated membranous nephropathy in a patient with neurofibromatosis type 1. *Eur J Med Genet*. 2018;61(2):84-88.