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CASE REPORT | COLON

Villous Adenoma: A Rare Cause of Neural Epidermal Growth Factor-Like 1-Positive Membranous Nephropathy

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ABSTRACT

We report the case of a 70-year-old woman diagnosed with neural epidermal growth factor-like 1 antigen-positive membranous nephropathy and nephrotic syndrome. Following thorough exclusion of autoimmune diseases, medications, or infections as potential causes, colonoscopy was performed as part of malignancy evaluation, revealing an 18 mm villous adenoma in the sigmoid colon and a 7 mm tubulovillous adenoma in the cecum. Despite the absence of gastrointestinal symptoms initially and the absence of high-grade dysplasia in the pathology report, the patient experienced a remarkable improvement in symptoms and a reduction in nephrotic-range proteinuria following polypectomy, observed within a few months.

KEYWORDS: villous adenoma; colonoscopy; membranous nephropathy

INTRODUCTION

Membranous nephropathy (MN) is a prevalent cause of nephrotic syndrome in adults, typically arising from antibody formation against glomerular antigens like neural epidermal growth factor-like 1 (NELL-1). While often idiopathic, secondary triggers encompass infections, autoimmune diseases, medications, and malignancies. Identifying the underlying cause is pivotal, as addressing it can promptly resolve MN without resorting to steroids or immunosuppressants. We present an unusual scenario where NELL-1-positive MN stemmed from a precancerous condition (colon polyp) rather than an outright malignancy.

CASE REPORT

A 70-year-old woman with a history of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome presented to her primary care clinic with progressively worsening severe bilateral lower extremity edema for 1 month, accompanied by increasing fatigue and loss of appetite. She denied experiencing shortness of breath, orthopnea, abdominal pain, nausea, vomiting, diarrhea, or melena. Her surgical and family histories were noncontributory. She did not smoke, consume alcohol, or use illicit drugs. She took hydroxychloroquine 200 mg daily.

Her vital signs were within normal range, except for a blood pressure of 155/74 mm Hg. Physical examination revealed an elderly appearing woman with anasarca and scattered telangiectasias on the face but otherwise unremarkable. Routine blood work, including a complete blood count and comprehensive metabolic profile, were within normal ranges, except for a low total protein level of 5.2 g/dL (normal range: 6–8.3) and low albumin of 2.7 g/dL (normal range: 3.5–5.5). Urinalysis was negative for hematuria, pyuria, casts, or crystals but showed proteinuria. Twenty-four-hour urine quantitative analysis revealed 4.98 g of proteinuria. Serum and urine protein electrophoresis did not indicate the presence of monoclonal proteins. Serum A1c, C-reactive protein, and complement C3 and C4 levels were within the reference ranges.

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Kidney biopsy revealed NELL-1 antigen-positive MN. Phospholipase A2 receptor antigen staining was negative. Serologies for hepatitis B, hepatitis C, and HIV were negative. Autoimmune testing for lupus, Sjogren syndrome, scleroderma, and mixed connective tissue disease were negative. Anti-centromere antibodies were positive, consistent with her long-standing history of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome. Based on NELL-1 antigen positivity and negative autoimmune test results, there was concern for secondary malignancy or premalignant conditions. Because of the patient's age and risk profile, treatment with steroids or immunosuppressants was deferred pending further diagnostic workup.

A colonoscopy performed to exclude malignancy revealed an 18 mm polyp in the sigmoid colon (Figure 1) and a 7 mm polyp in the cecum (Figure 2), followed by hot snare polypectomy for removal of both polyps. Pathology reports identified the sigmoid polyp as a villous adenoma and the cecal polyp as a tubulovillous adenoma.

Follow-up tests for serum albumin, total protein, and 24-hour urine protein were conducted at 2 and 3 months after colonoscopy and polypectomy (Table 1). Her 24-hour urine protein improved to 3.86 g at 2 months and 2.2 g at 3 months without steroid or immunosuppressant use. At the 3-month follow-up visit, her bilateral lower extremity edema had markedly improved, and she had returned to normal appetite and baseline functioning.

DISCUSSION

MN is the leading cause of nephrotic syndrome in nondiabetic adults worldwide.[1] MN can be primary (75%–80% of cases) or secondary (20%–25% of cases).[2] Primary MN results from an autoimmune response to various glomerular antigens without secondary etiologies, whereas secondary MN occurs from infections (such as hepatitis B and HIV), autoimmune diseases (like lupus), malignancies, and medications (including nonsteroidal anti-inflammatory drugs, penicillamine, and captopril).[3] The commonly implicated glomerular antigens in MN are the phospholipase A2 receptor and thrombospondin type

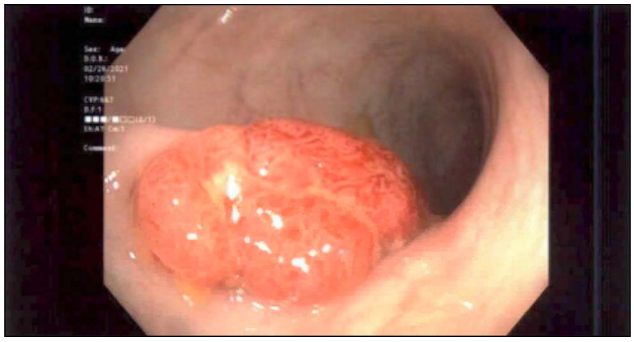

Figure 1. Colonoscopy showing an 18 mm polyp in the sigmoid colon.

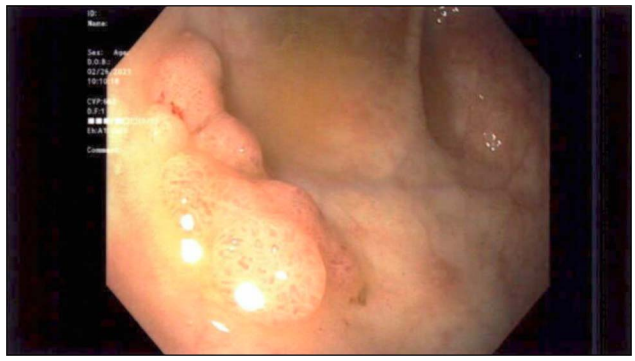

Figure 2. Colonoscopy showing a 7 mm polyp in the cecum.

1 domain-containing 7A, responsible for approximately 75% of MN cases.[2,3] Recent advances have identified new antigens, such as NELL-1, also involved in MN.[2]

NELL-1 is a cytoplasmic protein kinase C-binding protein, typically found in osteoblasts and renal tubules as well as glomeruli.[2] MN due to NELL-1 antigen is usually primary but can be secondary to malignancy in <30% of cases.[4] It typically occurs in individuals aged 50–70 years.[2] According to a study evaluating 30 patients with malignancies causing NELL-1-positive MN, most were solid organ malignancies and were advanced carcinomas; none included a precancerous condition.[4]

Adenomatous colon polyps fall into 3 classifications: tubular, villous, or tubulovillous, determined by the presence of villous features (finger-like or leaf-like epithelial projections observed in histology).[5] Villous adenomas, particularly those exceeding 1 cm in size, carry a heightened risk of dysplasia and malignancy (41%) in contrast to tubular adenomas (5%).[5,6] Though often asymptomatic, villous adenomas can cause abdominal cramps or bleeding to the rare occurrence of McKittrick-Wheelock syndrome, characterized by chloride-secreting diarrhea, hypokalemia, and metabolic alkalosis.[7] While rare reports exist of NELL-1-positive MN in benign or slow-growing tumors like neuroendocrine tumors and leiomyomas, this case represents the first known instance of a precancerous colon polyp causing NELL-1-positive MN to our knowledge.[8]

Clinicians often feel compelled to initiate immunosuppressive therapy due to severe symptoms of nephrotic syndrome; however, they carry numerous adverse effects, especially in elderly patients. Our case underscores the importance of screening patients with NELL-1-positive MN for secondary causes, particularly underlying malignancy. Addressing the underlying etiology leads to rapid resolution of nephrotic syndrome, obviating the need for steroids or immunosuppressants.

Colonoscopy, a widely practiced procedure by gastroenterologists worldwide, remains the gold standard for colon polyps or cancer screening. Current recommendations advocate colonoscopy screening for colon cancer in adults aged 45 years and older with an average lifetime risk.[9] However,

Table 1. Trend in proteinuria and serum proteins after removal of villous adenoma

Lab reports	At baseline	2 months after colonoscopy	3 months after colonoscopy
Serum albumin (g/dL)	2.7	2.8	3.1
Serum albumin/globulin ratio	1:1	1:3	1:3
Serum protein (g/dL)	5.2	5.0	5.5
Urine 24-hour protein (mg/24 hr)	4,988	3,864	2,206
24-hr Urine creatinine(gm/24 hr)	0.7	0.6	0.5
24-hr Urine protein/creatinine	7,345	6,292	4,663
eGFR non-AA (mL/min/1.73 m^2)	89	92	89

eGFR, estimated glomerular filtration rate.

according to a US Department of Health and Human Services survey, only 64.8% of adults older than 40 years undergo age-appropriate screening.[10] Our patient did not undergo screening colonoscopy until the age of 70. Although it is exceedingly rare for a villous adenoma to cause NELL-1-positive MN, in retrospect, a simple screening colonoscopy could have prevented significant medical complications and associated morbidity.

Finally, we underscore the significance of benign or precancerous conditions as important etiologies for MN and nephrotic syndrome. Given the widespread prevalence of colon polyps in the adult population, even among those at average risk, colonoscopy should be considered for all patients with MN when assessing secondary causes.

DISCLOSURES

Author contributions: R. Modi: case report writing, proofreading and review of data. G. Erazo: case report writing and proof reading. R. Anand: proof reading for critically important intellectual content, guidance, supervision, and final approval. R. Modi is the article guarantor.

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