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Membranous Glomerulonephritis as an Uncommon Presentation of Secondary Syphilis: A Reminder on Therapeutic Decision-Making in Clinical Practice

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Abstract

Membranous glomerulonephritis is one of the common causes of nephrotic syndrome in the adult population. It is idiopathic in the majority of patients, but the secondary forms can be seen in the setting of autoimmune disease, cancer, infection, and following exposure to certain medications. However, subclinical syphilis-related membranous nephropathy remains a particularly rare clinicopathologic entity in modern times. In this article, we chronicle an interesting case of latent syphilis masquerading as membranous glomerulonephritis, which resolved with benzathine penicillin without requiring immunosuppressive treatment. We further supplement this paper with a concise review of the relevant literature that delineates the utility of appropriate antibiotic therapy in the management of luetic membranous nephropathy. Clinicians should remain cognizant of secondary syphilis while evaluating patients for possible glomerulonephritis or those presenting with proteinuria. Additionally, patients with hepatitis B, hepatitis C, and human immunodeficiency virus infections are not infrequently coinfected with *Treponema pallidum*. Therefore, a high index of suspicion for systemic manifestations of syphilis such as nephrotic syndrome is warranted in the setting of a coinfection. Prompt diagnosis and treatment of syphilis may result in resolution of proteinuria, without the need for standard immunosuppressive therapy commonly used in clinical practice.

Keywords

membranous glomerulonephritis, secondary syphilis, nephrotic syndrome, proteinuria, unique presentation, therapeutic decision-making, antibiotic treatment

Introduction

While the systemic manifestations of a syphilis infection are increasingly reported, cases detailing luetic membranous glomerulonephritis remain relatively uncommon.[1,2] Syphilis-associated membranous nephropathy presents as a nephrotic syndrome with varying degrees of proteinuria.[3] It is currently understood that the antibody response mounted against *Treponema pallidum* results in the deposition of immunoglobulin G (IgG) in the renal mesangium, which in turn heralds the onset of nephropathy.[3] Even though merely a handful of cases of luetic membranous glomerulonephritis are documented in the past 2 decades, this association can have a multitude of clinical implications.[4] For instance, syphilis is seldom seen today in the United States, with most of the cases detected primarily in human immunodeficiency virus (HIV)-positive individuals.[5] As hepatitis B, hepatitis C, and HIV infections can also orchestrate membranous nephropathy, this great "imitator" might therefore evade detection.[6,7] Consequently, the membranous nephropathy may wrongly be attributed to hepatitis or HIV itself in patients who are simultaneously positive for these viral infections and syphilis. Therefore, a high index of clinical suspicion is warranted for precise etiology establishment, especially in patients with a coinfection.

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In luetic nephropathy, massive proteinuria is often observed, and treatment with an appropriate antibiotic is required. However, in clinical practice, specific immunosuppressive regimens are commonly commenced to thwart the pathogenesis underlying the membranous nephropathy.[8] Clinicians should consider the possibility of deterioration with corticosteroid treatment in cases with subclinical syphilis-related nephrotic syndrome.[9] Thus, self-confined membranous nephropathy secondary to syphilis warrants due attention from nephrologists and venereal experts as the treatment approach is different in such cases.[9] This leads us to the general consensus that for the prompt management and resolution of the luetic nephropathy precipitating proteinuria, a timely diagnosis and appropriate intervention is imperative.[9] We herein describe the case of an HIV-positive patient who presented with subclinical syphilis and concomitant early-stage membranous glomerulonephritis. The nephropathy was self-contained, and resolved with syphilis treatment, without any conventional immunosuppressive therapy. Furthermore, we review the medical literature regarding this association, focusing on the therapeutic decision-making in these patients. It is pertinent to highlight this particular duo because it may represent a diagnostic and therapeutic dilemma and more such cases can be encountered due to the reemergence of syphilis worldwide.

Case Presentation

This study involves a 21-year-old African-American male who was admitted to our medical center with the complaints of epigastric pain, nausea, vomiting, and diarrhea for 1 week. His medical history was significant for HIV, which was treated with highly active antiretroviral therapy. Review of systems was unremarkable for abnormalities. Sexual history was positive for a single male partner of less than a year. There was no history of previous renal disease, weight loss, arthralgia, dysuria, gross hematuria, or fever. He denied prior gastrointestinal disorders, upper respiratory tract infections, systemic allergies, and malignancies. He was a nonsmoker, nonalcoholic, and drug-free. His family history was negative for cancer and renal disorders. At presentation, the patient was afebrile and normotensive. Physical examination revealed a maculopapular rash on the trunk. A few small axillary and inguinal lymph nodes were palpable, with epigastric and perianal tenderness. In addition, 1+ edema was noted in his legs.

Investigations

Laboratory evaluation showed serum creatinine 7.4 mg/dL (baseline = 1.1 mg/dL) and blood urea nitrogen 53 mg/dL (7-20 mg/dL). Serum concentrations of electrolytes, transaminases, alkaline phosphatase, bilirubin, amylase, and lipase were normal. Total serum protein was initially 8.0 g/dL (6-8.3 g/dL), with a serum albumin level of 2.4 g/dL (3.4-5.4 g/dL). Urinalysis showed trace ketones, 4+ proteins, 2+ blood, whereas it was negative for nitrite and bacteria. Urine microscopy and culture were unremarkable. Urine protein/creatinine ratio was 7.3 g/gCre (<0.2 g/gCre). Infectious profile was positive for HIV with a viral load of 1917 copies/mL and CD4 count at 306 cells/mm^3 (500-1500 cells/mm^3). His rapid plasma reagin test was strongly positive. Serological test results for hepatitis C virus and hepatitis B virus turned out negative.

Immunologic testing including, antibodies to phospholipase A receptors (anti-PLA2R), cytoplasmic-antineutrophil cytoplasm antibodies (c-ANCA), perinuclear-ANCA (p-ANCA), myeloperoxidase-ANCA (MPO-ANCA), and antiproteinase 3-ANCA (PR3-ANCA) were negative. Furthermore, rheumatoid factor, anti-glomerular basement membrane, anti–Sjögren's-syndrome–related antigen A, anti-apoptosis signal-regulating kinase 1, anti–double stranded DNA, anti-smooth muscle, anti-streptolysin O titer, and anti-ribonucleoprotein particles antibodies were negative. Complement levels, thyroid function tests, lipid and coagulation profiles, and serum and urine protein electrophoresis were all within normal limits. Renal ultrasound showed no evidence of hydronephrosis, stones, or obstruction. Computed tomography scan of the abdomen without contrast revealed diffuse lymphadenopathy, fat stranding, edema in the perirectal area, generalized anasarca, and a small amount of ascites.

Renal Biopsy

Subsequently, an uneventful percutaneous renal biopsy was performed. The glomeruli had segmental, vague glomerular capillary wall "spikes" on the periodic acid–Schiff stain. The interstitium had a patchy plasmacytic infiltrate. Direct immunofluorescence with routine panel of antibodies (albumin, IgG, IgA, IgM, C1q, C3, fibrinogen, and kappa and lambda light chains) showed granular capillary staining with IgG, C3, and kappa and lambda light chains. On electron microscopy, numerous small subepithelial electron-dense immune-complex deposits were noted.

Diagnosis

The glomerular findings were consistent with an early-stage membranous glomerulonephritis. The interstitial plasmacytic infiltrate was not typical of an idiopathic membranous nephropathy. Given the HIV-positive status of the patient, HIV-associated nephropathy was initially considered plausible. However, a spirochete (treponemal) immunohistochemical stain was strongly positive for focal spirochete aggregates, within the areas of plasma cell-rich interstitial infiltrates, supporting the diagnosis of secondary membranous nephropathy following subclinical syphilis.

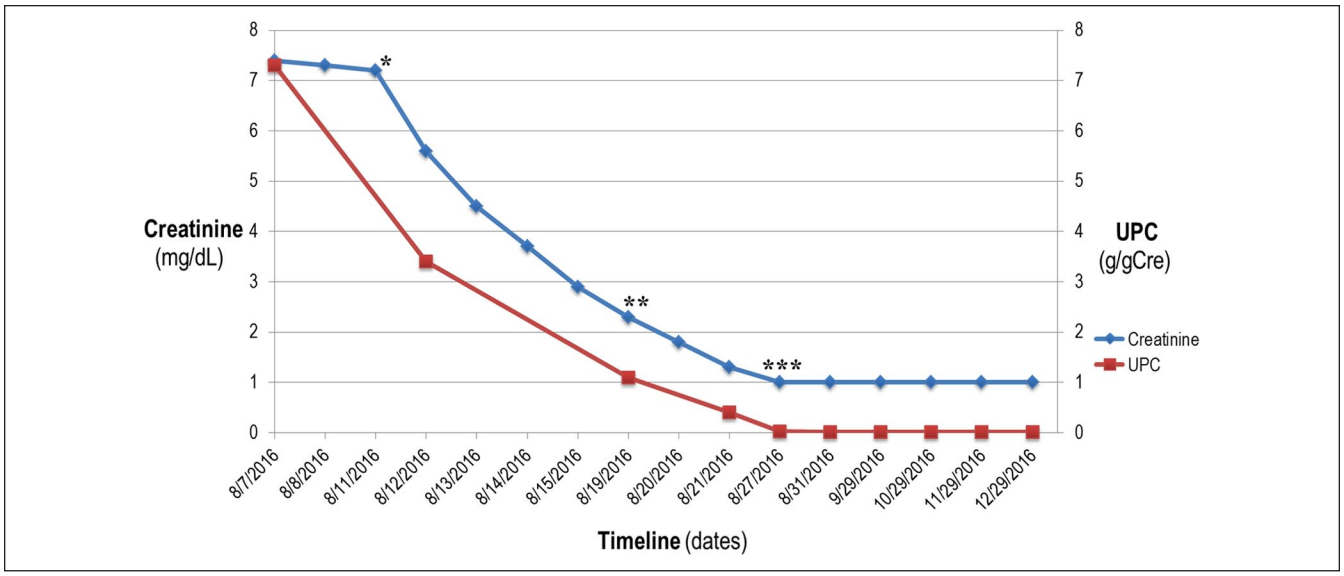

Figure 1. The line graph demonstrates resolution of luetic membranous glomerulonephritis after intramuscular benzathine penicillin 2.4 million units weekly for 3 weeks. As shown by the single star, August 11, 2016, was when the initial dose of penicillin was administered. The serum creatinine and urine protein/creatinine (UPC) levels started to decline immediately after the first dose. On August 19, 2016, as marked by the double star, the second dose of penicillin was administered. The levels of serum creatinine and UPC continued to fall. Subsequently, as depicted by the triple star, the third dose of penicillin was instituted on August 27, 2016. Thereafter, it resulted in the sustained normalization of renal parameters to the baseline levels of the patient.

Treatment and Clinical Outcome

The patient was immediately informed about his disease and was educated about the clinical importance of contact tracing. Prompt testing and treatment of his current and previous partners were recommended. He was then initiated on 3 weekly doses of intramuscular benzathine penicillin G 2.4 million units. His clinical symptoms resolved with conservative management and he was discharged home in a stable condition. At the 1-week follow-up, a significant improvement was evident in renal function with no treatment-related complications. At the outpatient clinic follow-up 4 weeks later, serum creatinine had returned to 1 mg/dL and the proteinuria had completely resolved as evidenced by a urine protein/creatinine ratio of 0.03 g/gCre. The patient demonstrated sustained recovery at the follow-up visit after 4 months (Figure 1).

Discussion

Membranous glomerulonephritis is an immune-mediated nephrotic syndrome that has the potential to progress to chronic kidney disease. It can either be primary or secondary as determined by the particular etiology and underlying pathogenesis. It is believed that 75% of the cases of membranous nephropathy are idiopathic.[10] In primary disease, M-type PLA2R, which are routinely found on podocytes, are implicated.[11] Notably, the etiology underlying secondary membranous glomerulonephritis is observed to be more diverse. Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, etc), infections (hepatitis B and C, and HIV), various cancers (lung cancer, prostate cancer, and hematological malignancies), and certain medications can be the underlying etiologies of secondary membranous nephropathy.[12] Syphilis has traditionally been termed the great mimicker owing to the potential of this disease to elicit a plethora of diverse systemic ramifications.[13] Of these systemic manifestations, luetic membranous nephropathy remains one of the less often encountered pathologies.[13] In the United States, it is reported that the prevalence of primary and secondary syphilis hovers around 9.5 per 100 000 populations.[14] Despite its resurgence in the Western world, syphilis is not routinely included in the differential diagnosis of membranous nephropathy.

We conducted a review of the English-language literature regarding secondary syphilis-related membranous nephropathy. The data on patient demographics, clinical characteristics, serum creatinine and proteinuria parameters, biopsy status, syphilis testing, and management were collected and summarized (Table 1). The mean age of patients was 22.16 years (range = 18-66 years). A clear gender predominance was noted, with 16 male and 2 female patients. Although a fixed geographical distribution is often difficult to ascertain, most patients were African American or Caucasians. Subclinical syphilis-related membranous nephropathy may present with a variety of symptoms, including facial and peripheral edema, maculopapular rash, lymphadenopathy, night sweating, unexplained weight gain, and/or gastrointestinal abnormalities.[15,16] Due to vague clinical symptomatology, the luetic nephropathy can possibly be incorrectly regarded as renal manifestation of other systemic diseases.[17,18] Notably,

Table 1. General Characteristics of Cases of Membranous Glomerulonephritis Secondary to Subclinical Syphilis.

Authors/year	Country	Age (years)/ gender	Clinical presentation	Comorbid conditions	Proteinuria (g/24 hours)	Serum creatinine (mg/dL)	Associated findings	Biopsy-proven MGN	Syphilis diagnosis	Treatment	Clinical outcome
Tang et al[19]/1989	USA	54/male	Postprandial vomiting and vague upper abdominal discomfort	DM, syphilitic hepatitis, gallstones	10	Not reported	Jaundice, maculopapular rash, lymphadenopathy, marked pitting edema up to the knees, abnormal LFTs	Yes	VDRL titer >1: 2048, TPHA titer >1: 20 400, FTA-ABS IgG and IgM +	Procaine penicillin IM 600 000 IU daily for 14 days	Recovered
Hunte et al[15]/1993	USA	21/male	Facial and peripheral edema, weight gain (15 lbs), skin rash, polyuria, polydipsia, myalgias, headaches, and sore throat	DM, HTN	>3	1.2	3+/4+ pretibial, pedal and hand pitting edema, glycosuria without acetonuria, and nonpruritic eruption over the forearms, trunk, and feet	Yes	RPR markedly elevated 1:1024, FTA-ABS 4+	Benzathine penicillin 2.4 million U IM weekly for 3 weeks	Recovered
Soehardy et al[24]/2006	Malaysia	31/male	Facial puffiness and bilateral leg swelling	Unprotected sex	9.7	0.85	Sacral edema, reduced urine output, and frothy urine	Yes	VDRL 1:32, syphilis IgG and IgM+	Benzathine penicillin 2.4 million U IM weekly for 3 weeks	Recovered
Gooskens et al[18]/2008	The Netherlands	58/male	Intermittent bloody stools, abdominal pain, and chronic diarrhea	Unprotected sex, *Chlamydia trachomatis* urethritis, and syphilitic GI symptoms	3.78	<1.2	Discrete skin rash on proximal upper extremities	Yes	VDRL titer 1:64, TPHA+, and *Treponema pallidum* immunoblot+	Benzathine penicillin G 2.4 million U IM	Recovered
Satoskar et al[17]/2010	USA	18/female	Nausea and vomiting	Gynecological bleeding and infantile thoracic neuroblastoma	>3	0.9	Facial (3+) and symmetrical lower-extremity (1+) edema, no rash	Yes	RPR+, FTA−, and ABS+	Corticosteroid, mycophenolate mofetil, high-dose, IM penicillin in 3 weekly injections	Recovered
Havill et al[40]/2011	USA	20/male	Pain in the right flank	HIV infection	4.8	5.2	A diffuse maculopapular rash involving trunk, extremities, palms and soles, and hepatosplenomegaly	Yes	RPR titer 1:128, *Treponema pallidum* IgM and IgG+	Benzathine penicillin 2.4 million U IM	Recovered

(continued)

Table 1. (continued)

Authors/year	Country	Age (years)/ gender	Clinical presentation	Comorbid conditions	Proteinuria (g/24 hours)	Serum creatinine (mg/dL)	Associated findings	Biopsy-proven MGN	Syphilis diagnosis	Treatment	Clinical outcome
Handoko et al[16]/2011	The Netherlands	Late 30s/ male	Malaise, myalgia, headache, sore throat, lymphadenopathy, and night sweating	Prior anabolic steroid use as afitness regimen	16.8	1.3	Weight gain (10 lbs in 1 week), pedal edema, swollen eyelids, non-itching, and painless "rash" on his glans penis	Yes	VDRL titer of 1:64, *Treponema pallidum* CLIA and IgG blot+	Benzathine penicillin 2.4 million U IM	Recovered
Canney et al[20]/2011	Australia	41/male	Drenching night sweats, widespread nonpruritic rash, and facial edema	Syphilitic hepatitis and unprotected sex	21.96	1.4	Pitting lower limb and sacral edema, frothy urine, hepatomegaly, and elevated LFTs	Yes	RPR 1:128	Intravenous benzylpenicillin (1.8 g every 4 hours)	Recovered
Mora Mora et al[25]/2011	Spain	27/male	Edema of the lower limbs and genitals, and decreased diuresis	Cryptorchidism, adenoidectomy, and amygdalectomy	13.4	1.73	Slight pharyngodynia, right groin induration, penile ulcer, and maculopapular lesions on trunk and extremities	Yes	RPR 1:32, FTA-ABS+	Benzathine penicillin G 2.4 million U IM	Recovered
Hannawi et al[38]/2012	USA	24/male	Progressive bilateral lower extremity edema	Tonsillectomy	0.76	1.1	Weight gain (8 lbs), dyspnea, painless chancre on genitals, and small hyperpigmented leg macules	Yes	RPR 1:512, TP-PA+	Benzathine penicillin G 2.4 million U IM 3 weekly injections	Recovered
Ishiwatari et al[21]/2012	Japan	66/male	Peripheral edema and increasing general fatigue	Syphilitic hepatitis	19 g	2.15	Penile swelling and induration, sore throat, general fatigue, and a nonpruritic eruption on the arms and back	Yes	RPR 1:128, TPHA 1:41.2	Amoxicillin for 14 days	Recovered
Cheng et al[37]/2015	Taiwan	23/male	Pitting leg edema and glans penis ulcer	Drug abuse, unprotected sex, and HIV infection	13.8	0.81	Skin rash on extremities	Yes	RPR: 4144 RU, TPHA: 2310 TU	Intravenous benzathine penicillin	Recovered
Noutong et al[27]/2016	USA	51/male	Lower back pain	HTN and seizure disorder	4.9	6.09	Red lesions on the mucous membrane of soft palate and maculopapular rashes on the palms and the soles	Yes	RPR 1:512, FTA-ABS+	Penicillin G, 2.4 million U IM	Recovered

(continued)

Table 1. (continued)

Authors/year	Country	Age (years)/ gender	Clinical presentation	Comorbid conditions	Proteinuria (g/24 hours)	Serum creatinine (mg/dL)	Associated findings	Biopsy-proven MGN	Syphilis diagnosis	Treatment	Clinical outcome
Makker et al[22]/2016	USA	51/male	Abdominal pain and bright red blood per rectum	DM, osteoarthritis, drug abuse, diastolic dysfunction, and luetic hepatitis	5.9	0.7	Nonbilious vomiting, copper-colored papules and macules on the body, and mild bilateral pitting pedal edema	Yes	RPR titer 1:1024	Benzathine penicillin G 2.4 million U IM	Recovered
Fernandes et al[26]/2017	Portugal	29/female	Small erythematous papules on the trunk and upper limbs, lower limb edema, and inguinal adenopathy	Not reported	5.3	Not reported	Hypoalbuminemia (1.1 g/dL), HCL (total cholesterol 363 mg/dL, LDL 252 mg/dL, triglycerides 305 mg/dL)	Yes	VDRL titer was 1/64; TPHA titer was 1/2560	Penicillin 2.4 million U IM	Recovered
Zhang et al[23]/2018	USA	37/male	Rectal pain, nausea, vomiting, dark urine, and nonbloody diarrhea	HIV infection, depression, and syphilitic hepatitis	8.2	1.4	Rectal ulcer, bilateral inguinal lymphadenopathy, and abnormal LFTs	Yes	RPR titer 1:16, FTA-ABS+	Benzathine penicillin 2400000 IU once per week for 3 weeks	Recovered
Sciaudone et al[39]/2019	USA	21/male	Myalgias, fever, nausea, and nonbilious vomiting	HIV infection and unprotected sex	>3	7.1	Dull, crampy abdominal pain, and dark urine	Yes	RPR titer 1:256, treponemal antigen+	Benzathine penicillin G 2.4 million U IM	Recovered
Sciaudone et al[39]/2019	USA	35/male	Abdominal pain, nausea, periodic emesis, and right upper quadrant and right flank pain	HIV infection	>3	3.2	Diffuse papular, nonpruritic, nontender rash, and mildly elevated LFTs	Yes	RPR titer 1:128, treponemal antigen+	Benzathine penicillin G 2.4 million U IM	Recovered
The present report	USA	21/male	Epigastric pain, nausea, vomiting, and diarrhea	HIV infection	7.3	7.4	Maculopapular rash on trunk, a few small palpable axillary and inguinal lymph nodes, and 1+ edema in legs	Yes	Strongly positive RPR	IM penicillin G benzathine 2.4 million U in 3 doses over 3 weeks	Recovered

Abbreviations: MGN, membranous glomerulonephritis; DM, diabetes mellitus; LFTs, liver function tests; VDRL test, venereal disease research laboratory test; TPHA, *Treponema pallidum* particle agglutination assay; FTA-ABS, fluorescent treponemal antibody-absorption test; Ig, immunoglobulin; IM, intramuscular; HTN, hypertension; RPR, rapid plasma reagin; GI, gastrointestinal; CLIA, chemiluminescence immunoassay; HIV, human immunodeficiency virus; TP-PA, *Treponema pallidum* particle agglutination; HCL, hypercholesterolemia; LDL, low-density lipoprotein.

patients with syphilitic nephropathy may also concurrently develop acute hepatitis.[19-23] Given the possibility of deranged hepatic function, liver function testing is important. Furthermore, a detailed clinical history, especially information regarding safer sex practices, is pertinent in these patients.[24-26] Laboratory evaluation shows significant proteinuria as well as elevations in serum creatinine levels in most cases.[27] However, a few patients may also have baseline serum creatinine levels with no proteinuria at the initial presentation. Additionally, other abnormalities such as hypoalbuminemia or abnormal lipid profile should also be considered. In patients with secondary membranous glomerulonephritis, screening and confirmatory serological workup for syphilis should be mandated. An apt and prompt discernment of the etiology underlying proteinuria is therefore pivotal in governing the treatment regimens.

In terms of biopsy findings, membranous nephropathy is often characterized by diffuse capillary and basement membrane thickening. Immunofluorescence often divulges a granular appearance due to immune-complex deposits.[28] On electron microscopy, a "spike and dome" appearance, which represents subepithelial immune-complex deposition, can be appreciated.[28] In patients with syphilis infection, anti-treponemal IgG antibodies are produced and subsequently deposit in the subepithelial layer of the glomerular basement membrane.[29] In syphilis-induced nephropathy, C3 complement levels also rise in conjunction with IgG and IgM antibodies.[29] Therefore, luetic membranous nephropathy ensues in the aftermath of immune-mediated podocyte injury. Thus, the treatment should mainly be tailored toward treating syphilis as it is the potent trigger leading to immune response, culminating in membranous nephropathy in such patients.

A majority of case reports suggest that the membranous glomerulonephritis associated with syphilis infection is readily reversible with penicillin therapy alone, thereby potentially avoiding the need for immunosuppressive agents or even renal replacement therapy. Penicillin G remains the antibiotic of choice in treating a syphilis infection owing to remarkable susceptibility of *Treponema pallidum* to this drug.[30] The mode of administration often varies in accordance with the disease stage. However, for primary, secondary, and tertiary syphilis, intramuscular injection containing benzathine penicillin G (2.4 million units) remains the ideal therapeutic choice in most cases.[31] While data to support the use of alternatives to penicillin remains limited, options for non-pregnant patients who are allergic to penicillin may include doxycycline, tetracycline, and for neurosyphilis, ceftriaxone.[31] With regard to the stages of syphilis, a detailed venereal history remains pivotal, which may indicate the timeline of infection, providing invaluable cues to the disease progress. In its tertiary stage, for instance, syphilis may manifest debilitating neurological and cardiological repercussions, and prompt treatment aimed particularly toward the disease process is exceedingly imperative.[32] Additionally, the Jarisch-Herxheimer reaction, which ensues in the aftermath of penicillin administration and subsequently results in constitutional symptoms amid a treponemal infection, should also be considered.[33] For individual patient symptoms, conservative management may be considered. In addition, diuretics such as frusemide are employed to improve edema, and an angiotensin-II receptor blocker can also be administered for its anti-proteinuric effect.[34]

Due to the presence of a multitude of variables that may confound patient presentation, commencement of inappropriate initial treatment in the context of luetic membranous nephropathy is possible. For instance, steroids are conventionally employed for the treatment of membranous glomerulonephritis. However, if steroids are instituted for treating patients afflicted with membranous glomerulonephritis secondary to syphilis, adverse outcomes may ensue that may advance the stage of syphilis.[35] By suppressing the immune system, steroids can interfere with the natural process of infection-containment, thereby delaying recovery from luetic nephropathy. Thus, it is better to screen for syphilis before initiation of immunosuppressive treatment even among patients with primary membranous glomerulopathy.[36] The underlying etiology in turn governs the eventual management. A meticulous workup should be duly conducted to deduce the definitive underlying cause in order to institute appropriate medical treatment.

This article highlights several important clinical implications of luetic nephropathy. It illustrates that the immunostaining markers, including anti-treponemal IgG, should be carefully evaluated in patients presenting with nephrotic-range proteinuria. Along the same chain of thought, a self-resolving nephritis also does not preclude the diagnosis of a luetic membranous nephropathy. Furthermore, this article points to the riveting possibility of a syphilis infection in patients concomitantly afflicted with a hepatitis B virus, hepatitis C virus, or HIV coinfection.[37-40] Since HIV and hepatitis may also cause membranous glomerulonephritis, luetic nephropathy might incorrectly be attributed to the presence of these infectious diseases, obscuring the true diagnosis and rendering prompt treatment dilatory.[6,7,41] In addition, syphilis is a reemerging disease; global statistics show about 10 000 new cases every year.[42] Therefore, a syphilis-induced, self-resolving membranous nephropathy should be borne in mind in order to appropriately decide treatment and to yield fecund clinical outcomes.

Learning Points

- This study highlights membranous glomerulonephritis in concoction with secondary syphilis and it serves the purpose of community awareness regarding this potential association as initial presentation may cause much confusion and concern in such cases.
- Clinicians should remain vigilant for syphilis as a possible, albeit rare, cause of proteinuria or nephrotic

syndrome. An exhaustive search should be carried out to identify this secondary cause of membranous glomerulonephritis. Detailed history taking focusing on sexual history, careful review of clinical features, and morphological and immunostaining biopsy findings are imperative.

- In such patients, mandatory serological testing for syphilis should be conducted regardless of the clinical course and histopathologic pattern.
- With regard to therapeutic approaches, an updated knowledge of this uncommon presentation of syphilis is of paramount importance as membranous glomerulonephritis may show clinical remission with the treatment of underlying syphilis alone, without the need for immunosuppressive therapy.
- Immunosuppressive drugs such as corticosteroids may show a propensity to complicate an otherwise self-limited luetic membranous nephropathy. Therefore, therapeutic decision-making should be carefully deliberated upon in these patients.

Authors' Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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References

1. Magarian GJ, Marr C. Secondary syphilis presenting as nephrotic syndrome. *West J Med*. 1992;156:654-655.
2. Abitbol CL, Friedman LB, Zilleruelo G. Renal manifestations of sexually transmitted diseases: sexually transmitted diseases and the kidney. *Adolesc Med Clin*. 2005;16:45-65.
3. Lai WL, Yeh TH, Chen PM, et al. Membranous nephropathy: a review on the pathogenesis, diagnosis, and treatment. *J Formos Med Assoc*. 2015;114:102-111.
4. Couser WG, Johnson RJ. The etiology of glomerulonephritis: roles of infection and autoimmunity. *Kidney Int*. 2014;86:905-914.
5. Blocker ME, Levine WC, St Louis ME. HIV prevalence in patients with syphilis, United States. *Sex Transm Dis*. 2000;27:53-59.
6. Iovănescu VF, Constantinescu AF, Streba CT, et al. Clinical and pathological considerations on renal diseases in patients with chronic viral hepatitis. *Rom J Morphol Embryol*. 2016;57:401-406.
7. Kudose S, Santoriello D, Bomback AS, et al. The spectrum of kidney biopsy findings in HIV-infected patients in the modern era. *Kidney Int*. 2020;97:1006-1016.
8. Cattran D, Brenchley P. Membranous nephropathy: thinking through the therapeutic options. *Nephrol Dial Transplant*. 2017;32:22-29.
9. Nasr SH, Radhakrishnan J, D'Agati VD. Bacterial infection-related glomerulonephritis in adults. *Kidney Int*. 2013;83:792-803.
10. Abe S, Amagasaki Y, Konishi K, Kato E, Iyori S, Sakaguchi H. Idiopathic membranous glomerulonephritis: aspects of geographical differences. *J Clin Pathol*. 1986;39:1193-1198.
11. van de Logt AE, Fresquet M, Wetzels JF, Brenchley P. The anti-PLA2R antibody in membranous nephropathy: what we know and what remains a decade after its discovery. *Kidney Int*. 2019;96:1292-1302.
12. KDIGO Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int*. 2012;2(suppl 2):186-197.
13. Goh BT. Syphilis in adults. *Sex Transm Infect*. 2005;81:448-452.
14. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2017. Syphilis. Accessed July 22, 2020. https://www.cdc.gov/std/stats17/syphilis.htm
15. Hunte W, al-Ghraoui F, Cohen RJ. Secondary syphilis and the nephrotic syndrome. *J Am Soc Nephrol*. 1993;3:1351-1355.
16. Handoko ML, Duijvestein M, Scheepstra CG, de Fijter CWH. Syphilis: a reversible cause of nephrotic syndrome. *BMJ Case Rep*. 2013;2013:bcr2012008279.
17. Satoskar AA, Kovach P, O'Reilly K, Nadasdy T. An uncommon cause of membranous glomerulonephritis. *Am J Kidney Dis*. 2010;55:386-390.
18. Gooskens J, Coenraad MJ, Groeneveld JH, Prins FA, Smit VTHBM. Clinical challenges and images in GI. Syphilitic sigmoiditis complicated by membranous nephropathy. *Gastroenterology*. 2008;135:363-716.
19. Tang AL, Thin RN, Croft DN. Nephrotic syndrome and hepatitis in early syphilis. *Postgrad Med J*. 1989;65:14-15.
20. Canney M, Liu E, Vonthethoff L, Weatherall C, Ong S. Nephrotic syndrome and hepatitis due to acquired syphilis: an uncommon presentation of a re-emerging disease. *NDT Plus*. 2011;4:67-70.
21. Ishiwatari A, Hasegawa J, Hoshino Y, Kaga T, Abe Y, Wakai S. Simultaneous nephrotic syndrome and hepatitis in secondary syphilis: case report and review of the literature. *CEN Case Rep*. 2015;4:223-227.
22. Makker J, Bajantri B, Nayudu SK. Secondary syphilis with hepatitis and nephrotic syndrome: a rare concurrence. *J Clin Med Res*. 2016;8:550-554.
23. Zhang Z, Hever A, Bhasin N, Kujubu DA. Secondary syphilis associated with membranous nephropathy and acute hepatitis in a patient with HIV: a case report. *Perm J*. 2018;22:17-062.

24. Soehardy Z, Hayati SN, Rozita M, et al. Subclinical acquired syphilis masquerading as membranous glomerulonephritis. *Med J Malaysia*. 2006;61:484-486.
25. Mora Mora MT, Domíngueza MSG, Cerviño MIC, Santana RN, Arroyo JRGM. Membranous glomerulonephritis in a patient with syphilis [in Spanish]. *Nefrologia*. 2011;31:372-373.
26. Fernandes AR, Gouveia F, Viegas MSR, et al. Self-limited membranous glomerulonephritis due to syphilis. *J Eur Acad Dermatol Venereol*. 2017;31:501-502.
27. Noutong SA, Chornyy V, Alquadan KF, Ejas AA, Koratala A. A red herring in the green grass: syphilitic membranous glomerulonephritis. *Am J Med*. 2017;130:285-287.
28. Beck LH, Salant DJ. Membranous nephropathy: recent travels and new roads ahead. *Kidney Int*. 2010;77:765-770.
29. Gamble CN, Reardon JP. Immunopathogenesis of syphilitic glomerulonephritis. Elution of antitreponemal antibody from glomerular immune-complex deposits. *New Engl J Med*. 1975;292:449-454.
30. Hook EW 3rd. Syphilis. *Lancet*. 2017;389:1550-1557.
31. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1-137.
32. Pastuszczak M, Wojas-Pelc A. Current standards for diagnosis and treatment of syphilis: selection of some practical issues, based on the European (IUSTI) and U.S. (CDC) guidelines. *Postepy Dermatol Alergol*. 2013;30:203-210.
33. Butler T. The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. *Am J Trop Med Hyg*. 2017;96:46-52.
34. Jeon J, Kim DH, Jang HR, et al. Urinary angiotensinogen as a surrogate marker predicting the antiproteinuric effects of angiotensin receptor blockers in patients with overt proteinuria: a multicenter prospective study. *BMC Nephrol*. 2020;21:180.
35. Pinto-Almeida T, Rosmaninho A, Sanches M, Alves R, Selores M. Secondary syphilis on a psoriatic patient under cyclosporine: a challenging case. *Int J Dermatol*. 2014;53:e35-e38.
36. Kaynar K, Güvercin B, Mungan S, Ulusoy S. Don't forget syphilis in membranous nephropathy before immunosuppressants: latent syphilis in a patient with proteinuria [in Spanish]. *Nefrologia*. Published online March 3, 2020. doi:10.1016/j.nefro.2019.12.001
37. Cheng YC, Ku WW, Wong WW, Yang AH, Li SY. The case a 23-year-old Asian man with HIV infection and leg pitting edema. *Kidney Int*. 2015;88:649-650.
38. Hannawi B, Raghavan R. Syphilis and kidney disease: a case report and review of literature. *Nephrol Res Rev*. 2012;4:45-47.
39. Sciaudone M, Rutstein SE, Farel CE. Syphilis-associated acute renal failure and hepatitis in the setting of human immunodeficiency virus coinfection. *Sex Transm Dis*. 2019;46:816-818.
40. Havill JP, Kuperman MB, Bernardo LL, Jaar BG. The case: an age-old enemy should not be forgotten. *Kidney Int*. 2011;79:924-925.
41. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int*. 2004;66:1145-1152.
42. Tong ML, Lin LR, Liu GL, et al. Factors associated with serological cure and the serofast state of HIV-negative patients with primary, secondary, latent, and tertiary syphilis. *PLoS One*. 2013;8:e70102.