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Case and Review

Cholestatic Hepatitis with Concomitant Nephrotic Syndrome due to Secondary Syphilis in a Young Man

Chun-Chi Yang[a] Jui-Yi Chen[b] Hsuan-Yuan Chang[a] Ming-Jen Sheu[a]
I-Che Feng[a] Su-Hung Wang[a] Hsing-Tao Kuo[a]

[a]Division of Hepatogastroenterology, Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan; [b]Division of Nephrology, Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan

Keywords
Syphilis · Syphilitic hepatitis · Nephrotic syndrome · Men who have sex with men

Abstract
Introduction: Syphilis, an ancient sexually transmitted disease, is recognized as a systemic infection disease manifesting with diverse symptoms and variations. Secondary syphilis characterized by systemic symptoms resulted from hematogenous and lymphatic dissemination of the infection, may include manifestations such as hepatitis and nephrotic syndrome. However, the simultaneous occurrence of hepatitis and nephrotic syndrome in secondary syphilis is rare. ***Case Presentation:*** A young man presented with fatigue, abnormal liver function tests, and hyperbilirubinemia and had history of men who have sex with men (MSM). Serological tests confirmed the diagnosis of secondary syphilis, and kidney biopsy indicated membranous nephritis. After antibiotic treatment, the patient experienced resolution of proteinuria, and liver enzyme levels returned to normal. ***Conclusion:*** Syphilis should be considered in the differential diagnosis of simultaneous liver and kidney dysfunction, particularly in patients engaging in high-risk sexual behavior. This case highlights the importance of considering syphilis in young patients with MSM and presenting with unexplained nephrotic syndrome and liver abnormalities.

Correspondence to:
Chun-Chi Yang, fanoiayang@gmail.com

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Introduction

Syphilis is a well-known disease caused by the pathogen *Treponema pallidum*. It was known as a sexually transmitted disease, transmitted not only through the genital tract but also potentially through mucosal damage during anal intercourse. It is a systemic disease with multiple symptoms and variations, which is so-called "the great imitator." The disease progresses through different stages with varying characteristics and symptoms, including primary, secondary, tertiary, and latent stages [1].

Primary syphilis is characterized by a painless, solid, indurated ulcerative skin lesion called chancre, which typically appears 2–6 weeks after infection and usually spontaneously subsides. Secondary syphilis presents with systemic symptoms resulted from a hematogenous and lymphatic dissemination of the infection, with a generalized maculopapular rash being the most characteristic finding. Otherwise, lymphadenopathy, fever, and malaise may develop in weeks to months after the initial infection. Tertiary syphilis eventually displays systemic manifestation, including cardiovascular, neurological symptoms, occurring years after the initial infection. Additionally, there is latent syphilis, which is asymptomatic and can only be confirmed by serological findings.

Syphilitic hepatitis and nephrotic syndrome are known complications of secondary syphilis, but their simultaneous occurrence is rare. In this case report, we aimed to introduce the presentation and clinical course of a patient experiencing syphilitic hepatitis concomitant with nephrotic syndrome.

Case Presentation

A 23-year-old man with an unremarkable medical history presented at the digestive outpatient clinic in our hospital, complaining of persistent fatigue for several weeks and one episode of near syncope yesterday. He also reported increasing abdominal pain and poor appetite over the past 2 weeks, and a previous hospital visit revealed abnormal liver function tests with combined hyperbilirubinemia. Abdominal ultrasound showed only moderate fatty liver disease without biliary tract obstruction. He was admitted for further evaluation and management.

Through an episode of syncope, he had normal consciousness without neurological signs at present. He denied chest pain, palpitation, positional hypotension, fever, chills, nausea, vomiting, arthralgia, body weight loss, history of renal disease, alcohol abuse, or illicit drug use. Physical examination revealed his height (181 cm), body weight (116 kg), blood pressure (193/120 mm Hg), pulse (98 beats per minute, regular), and body temperature (36.2°C). His liver and spleen were not palpable, and there was no sign of meningeal irritation or any other neurological abnormalities. Examination of the head and neck, lungs, heart, and abdomen were normal, and there was no evidence of uveitis on ophthalmic examination. The patient denied penile swelling or induration, and no skin eruption or rash was observed on the trunk or extremities, nor was there pitting edema in the limbs.

Laboratory findings revealed cholestasis with increased alanine aminotransferase of 211 U/L, aspartate aminotransferase of 101 U/L, total bilirubin of 1.41 mg/dL, direct bilirubin of 0.72 mg/dL. He had a low albumin level of 3.2 g/dL. White cell count of 8,000/μL, hemoglobin of 14.5 g/dL, blood urea nitrogen of 12 mg/dL, serum creatinine of 0.96 mg/dL were within the normal range. A workup for hepatitis of virological analyses was negative for viral hepatitis A, B, C, cytomegalovirus, Herpes simplex virus, and Epstein-Barr virus infection. Comprehensive workup for autoimmune and metabolic disorders was unremarkable. Liver MRI demonstrated mild fatty liver disease and borderline splenomegaly with size around 13 cm at the longest diameter, while there were no structural alterations of the kidneys.

However, urine protein (3+) was detected on routine dipstick urinalysis at admission. Subsequent quantitative urine protein examinations revealed an increased albumin creatinine ratio of 1,295.8 mg/g Cre and a urine protein creatinine ratio of 972.4 mg/g (<150 mg/g). The A/G ratio was 0.8.

Given the acute onset of proteinuria and persistent hypertension in a young man without renal impairment, we conducted investigations for atypical infections, viral infection, and sexually transmitted disease. The rapid plasma reagent (RPR) test showed a markedly reactive titer of 1:128, and a Treponema pallidum hemagglutination (TPHA) test was positive with an increased titer of 1:2,560. Human immunodeficiency virus (HIV) antibody test was negative. Serum immunoglobulin (Ig) G level was 1,570 mg/dL (normal range: 540–1,822 mg/dL), IgA was 407 mg/dL (63–484 mg/dL), IgM was 292 mg/dL (22–240 mg/dL), and IgE was 766 IU/mL (<100 IU/mL). The patient reported unprotected sexual contact with a new sexual partner in a homosexual relationship for 2 months, who was diagnosed with syphilis. However, our patient denied penile swelling and induration in the months before admission.

A diagnosis of nephrotic syndrome caused by secondary syphilis was strongly suspected. Kidney biopsy was performed during admission, which revealed 15 well-perfused, non-sclerosed glomeruli. Staining with hematoxylin and eosin, periodic acid-Schiff, and Jones methenamine silver showed focal segmental thickening of capillary loops, focal mild expansion of mesangial matrix, and mild tubular atrophy (shown in Fig. 1a, b). Direct immunofluorescence revealed moderate diffuse granular glomerular capillary wall staining for IgG, C1q, and C3, Kappa, and Lambda. The tentative diagnosis was immune complex-mediated membranous nephritis with full-house immunofluorescence staining (shown in Fig. 1c). Electron microscopy did not show definite electron-dense deposits along capillary loops or in the mesangium, but diffuse granular deposits along the glomerular basement membrane were identified in the immunofluorescence study. So minimal change with equivocal electron-dense deposits and early-stage membranous glomerulonephritis was suspected (shown in Fig. 1d).

Based on the patient's sexual history, serological markers of syphilis, urine analyses, and kidney biopsy results, a diagnosis of syphilitic hepatitis with concomitant nephrotic syndrome during the secondary syphilis stage was made. The patient received intramuscular administration of three doses of penicillin G benzathine (2.4 million units) once a week. Valsartan and pentoxifylline were prescribed for hypertension and proteinuria due to their antiproteinuric effects. A 4-week follow-up visit showed favorable responses to these treatments. Urine protein levels soon decreased; the urine protein creatinine ratio dropped from 972.4 mg/g to 268.5 mg/g 1 month later. Liver and biliary enzymes returned to normal after penicillin treatment, and nephrotic syndrome completely resolved with normalized urinary protein excretion around 3 months after treatment (94.7 mg/g). And the subsequent titer of RPR showed remarkable decline, decreasing from 1:128 to 1:16 4 months after antibiotic treatment (Clinical course shown in Fig. 2.).

Discussion

Syphilis is a systemic human disease caused by the spirochete *T. pallidum*, subspecies *pallidum* [1]. It has re-emerged as a global public health problem in the last decades, with increasing notification rates in the Asia-Pacific region [2]. Developing countries account for about 90% of the 12 million new syphilis cases annually, with approximately 4 million cases reported in Asia alone [3]. From a national surveillance program in China, syphilis increased from 0.2/100,000 cases in 1993 to 5.7/100,000 in 2005; high-risk groups like commercial sex workers and men who have sex with men (MSM) had syphilis in 1 in 5–10 cases [4]. North America and Western Europe have seen a significant surge in syphilis incidence since 2010,

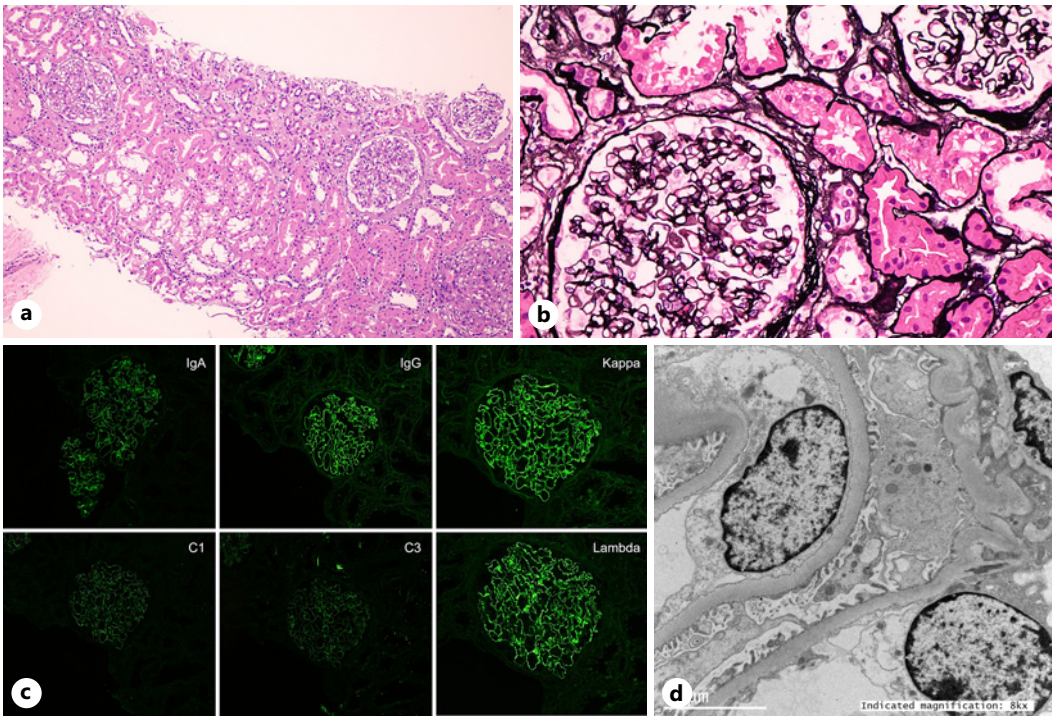
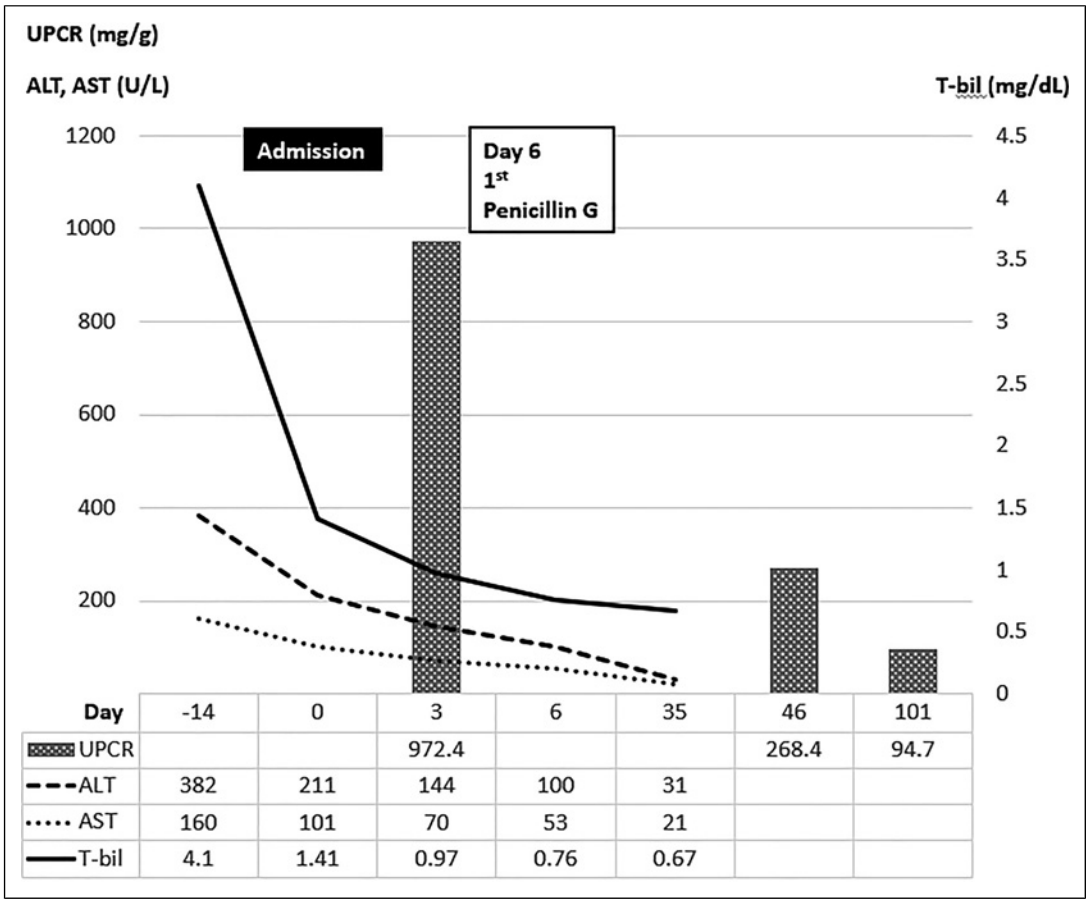


Fig. 1. Renal biopsy findings in patients with membranous glomerulonephritis (MGN). **a**, **b** Glomeruli exhibit focal segmental thickening of capillary loops, minimal tubular atrophy, and mild interstitial fibrosis. Mild interstitial inflammation is seen. There is no evidence of glomerular basement membrane spike formation (periodic acid-Schiff, original magnification 200). **c** Immunofluorescence staining for IgA, IgG, C1q, C3, Kappa, and Lambda reveals granular global glomerular capillary wall positivity, which is known as "full-house" deposition pattern and is typical seen in MGN. **d** Electron microscopy revealed minimal change with equivocal electron-dense deposits (arrowhead: microvilli transformation); early MGN was suspected.

particularly among MSM and individuals with concurrent HIV infection [1]. The risk factors that promote the re-emergence of syphilis include high-risk sexual activity, the proliferation of the sex industry, migration of workers, travel, and inadequate control measures [5]. Hence, there is an urgent need to refocus attention on diagnosing and treating this ancient disease.

Syphilis can affect multiple organs and present diverse clinical manifestations. Although rare, hepatitis can be a primary manifestation of syphilis, presented as liver enzyme abnormalities in cholestatic mode. A retrospective study conducted by E. Adachi revealed that 39% of early syphilis patients had liver enzyme abnormalities at the time of diagnosis [6]. While the overall incidence of syphilitic hepatitis (S.-H.W.) is quite low, S.-H.W. is estimated to occur in about 3% of secondary syphilis cases [6]. Crum-Cianflone et al. [7] reported that the occurrence of SH is common in some special populations, with approximately 38% of HIV-positive individuals with early-stage syphilis experiencing concurrent S.-H.W. Another cross-sectional study was conducted on HIV-infected individuals in Turkey; nine (6.4%) out of 141 syphilis-infected patients developed S.-H.W., and all of them were self-identified MSM [8]. One hypothesis regarding the pathogenesis of cholestatic pattern of liver injury in MSM-mediated SH may have possibly resulted from anal intercourse, leading to the migration of infection through the portal circulation and affecting the bile duct with further inflammation [9]. However, it is more commonly believed that the peri-cholangiolar inflammation observed in S.-H.W. is a partial result of the multisystemic involvement of immune-mediated mechanisms in response to the infection [6, 10].



Day	-14	0	3	6	35	46	101
UPCR			972.4			268.4	94.7
ALT	382	211	144	100	31		
AST	160	101	70	53	21		
T-bil	4.1	1.41	0.97	0.76	0.67		

Fig. 2. Clinical course.

Diagnostic criteria for SH, proposed by Mullick [10], include abnormal liver enzyme levels indicating hepatic involvement, serological evidence for syphilis with a positive TPHA titer consistent with primary or secondary syphilis, exclusion of alternative causes of hepatic injury and biliary tract diseases, and improvement in liver enzyme levels following appropriate antimicrobial therapy. And our case corresponds to the criteria mentioned above.

Another rare but well-recognized complication of secondary syphilis is nephrotic syndrome, which can be presented with hypoalbuminemia, proteinuria, hyperlipidemia, edema, and rapidly progressive nephritis. The association between syphilis and renal impairment has been reported since the early 1900s. One old case study in 1935 reported that the prevalence of nephrotic syndrome in early syphilis was 0.28% [11]. Immune complex deposition within the glomerulus mediated the damage to the nephron and tubules; membranous glomerulonephritis (MGN) is the most commonly observed histopathological finding in syphilis glomerulonephritis [12, 13]. Unlike idiopathic membranous nephropathy, MGN secondary to syphilis typically exhibits a "full-house pattern" on immunofluorescence studies of kidney biopsy, with staining not only for IgG and C3 but occasionally for IgA, IgM, and C1q [12]. The kidney biopsy in our case confirmed a diagnosis of early membranous nephropathy with the full-house pattern. Some patients are reported to have developed acute kidney injury but, in most cases, remained normal renal function. Syphilitic nephritis usually can be resolved with penicillin therapy, but sometimes hemodialysis, plasmapheresis, and methylprednisolone are required in the condition of rapidly progressive glomerulonephritis [14].

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Table 1. Literature review of ten cases presented with concomitant syphilitic hepatitis and nephrotic syndrome simultaneously

No. [Ref]	Clinical manifestation	Presentation		Pathology	
		liver	kidney	liver	kidney
1 McCracken 1969 [15] (1969)	Edema	None	Nephrotic syndrome	Active hepatitis	No biopsy
Bansal [16] (1978)	Fever, rash, edema	Elevated ALP	Nephrotic syndrome	Granulomatous hepatitis	MGN
Morrison [17] (1980)	Rash, edema	Elevated AST and ALT	Nephrotic syndrome	Granulomatous hepatitis	MGN
Tang [18] (1989)	Jaundice, rash, dyspnea	Elevated ALP and bilirubin	Nephrotic syndrome	No biopsy	MGN
Tang [19] (1999)	Edema, rash	Elevated ALP, AST, and ALT	Nephrotic syndrome	No biopsy	MGN, IgA nephropathy
Tsai [20] (2008)	Edema, general fatigue	Elevated AST and ALT	Nephrotic syndrome	No biopsy	Mild increase of mesangial matrix
Yoshikawa [21] (2014)	General malaise, loss appetite	Extremely elevated ALP	Nephrotic syndrome	Granulomatous hepatitis	Mesangial proliferation
Ishiwatari 2015 [22] (2015)	Edema, fatigue, rash	Elevated ALP, AST, and ALT	Nephrotic syndrome	No biopsy	MGN
Makker [23] (2016)	Abdominal pain, rash	Elevated ALP, AST, and ALT	Nephrotic syndrome	Chronic hepatitis	MGN
Kasper [24] (2020)	Myalgia, fever, rash, hair loos, BW loss	Near normal	Nephrotic syndrome	Periportal inflammation and histiocytic granuloma	No biopsy

Ref, reference; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; MGN, membranous glomerulonephritis.

While the liver and kidney can be involved during secondary syphilis, the concomitant occurrence of both hepatitis and nephrotic syndrome is extremely rare. To our knowledge, we had identified ten case reports from the literature documenting syphilitic hepatitis accompanied by nephrotic syndrome (Table 1) [15–24]. The most common manifestations were general malaise, edema, and skin rashes. Notably, the majority of cases showed a significant elevation in alkaline phosphatase (ALP), while hyperbilirubinemia was infrequent. The pattern of liver enzyme abnormalities is often cholestatic, and there are some other reported cases of SH demonstrating an extremely high level of ALP [25]. Mixed lymphoplasmacytic and granulocytic portal inflammation with variable bile duct injury and associated granulomas noted around the periportal and centrilobular regions could be revealed as the histopathologic change of SH in the liver [7]. These peri-cholangiolar inflammation may contribute to a cholestatic picture, offering an explanation for the significant elevation in ALP. Most cases displayed MGN or early changes of MGN on kidney biopsy, with granulomatous hepatitis being the most prominent finding on liver biopsy in half of the reported cases.

Conclusion

We present a rare case of syphilitic hepatitis concomitant with nephrotic syndrome in a young male patient with MSM. Syphilis remains a significant public health concern with re-emerging incidence in various regions worldwide. Timely recognition and appropriate management were instrumental in achieving a successful clinical outcome. This case report and literature review serve to increase awareness among healthcare professionals about the potential overlap of syphilis with diverse clinical presentations, emphasizing the significance of considering syphilis in the differential diagnosis of hepatic and renal disorders. Continued vigilance and research in this area are essential to enhance our understanding and management of such complex clinical scenarios. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537922).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Study approval was obtained from the patient. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Chun-Chi Yang and Jui-Yi Chen treated the patient. Chun-Chi Yang designed the research study and drafted the manuscript. Chun-Chi Yang, Jui-Yi Chen, and Hsuan-Yuan Chan contributed to the interpretation of the data. Ming-Jen Sheu, I-Che Feng, Su-Hung Wang, and Hsing-Tao Kuo participated in reviewing and making critical revisions to the manuscript. All authors read and approved the final version of the manuscript.

Data Availability Statement

The data that support the finding of this study are available from the corresponding author upon reasonable request. All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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