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# Syphilis and nephrotic syndrome: A case report and literature review

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ABSTRACT

A 31-year-old woman who had unprotected sexual intercourse with multiple partners presented to our hospital with bilateral leg edema, weight gain, and eyelid edema. One month before her visit, she had a fever of 38.0 ℃ for 2 days, and 1 week before her visit, she experienced fatigue. The presence of hypoalbuminemia, proteinuria, and leg edema raised the suspicion of nephrotic syndrome along with syphilis. She was treated with doxycycline for secondary nephrotic syndrome caused by secondary syphilis. Secondary syphilis is a well-known but rare cause of secondary nephrotic syndrome, and the occurrence rate, risk factors, and timing of occurrence are unknown. Therefore, we have supplemented this case report with a concise review of the relevant literature that delineates the use of appropriate antibiotic therapy in the management of secondary nephrotic syndrome derived from secondary syphilis.

## Background

Glomerular diseases may either be limited primarily to the kidney or associated with systemic conditions such as infections, autoimmune disorders, malignancy, and drug reactions. Glomerular diseases caused by infections include those caused by *Staphylococcus aureus*, Streptococci, hepatitis viruses, human immunodeficiency virus (HIV), and syphilis. Among these, syphilis, described as the "great masquerader," presents with a wide variety of symptoms. Nephrotic syndrome is a known but rare complication of secondary syphilis [1], and the occurrence rate, risk factors, and timing of occurrence are unknown. In Japan, the incidence rate of syphilis has recently risen [2], and the chances of encountering syphilis are potentially increasing. Here, we report a case of nephrotic syndrome that improved with appropriate treatment. We also conducted a literature review to investigate these questions.

## Case report

A 31-year-old woman presented with fatigue, weight gain, and lower extremity edema. One month prior, she had a fever of up to 38 ℃, which subsided naturally. One week prior, she developed headaches, nausea, and anorexia. Subsequently, she developed general malaise, edema of the face and bilateral lower legs, and a rapid weight gain of 8 kg. As her symptoms did not improve, she sought medical attention. During a review of systems, she admitted experiencing dizziness and sore throat but denied the occurrence of any other symptoms. She had a medical history of chlamydial urethritis that had been treated with azithromycin two years prior and no known drug allergies or medications; she did not use any illicit drugs. Her sexual history included multiple partners and unprotected sexual intercourse one to two times per week. Her body weight was 62 kg, an increase from the baseline value of 54 kg. Vital signs were stable, and physical examination revealed edema of the bilateral eyelids and lower extremities and bilateral cervical lymphadenopathies. Additionally, rash was observed on the bilateral forearms. The laboratory investigations revealed white blood cell counts 6300/μl, hemoglobin 18.3 g/dl, platelets 298,000/μl, serum creatinine level 1.89 mg/dl, total protein 4.8 g dl, albumin 1.3 g/dl. The urine creatinine/protein ratio was 10.9 g/g・Cre. Because TPHA and RPR were positive and the reactive plasma reagin (RPR) titer was as high as 1:32, we performed a lumbar puncture to rule out neurosyphilis; however, no evidence of meningitis was observed. HIV antigen/antibody was negative. Therefore, we initiated 100 mg of doxycycline, orally every 12 h for 14 days, to treat secondary syphilis along with nephrotic syndrome. Initially, a renal biopsy was planned, but after her edema and proteinuria improved dramatically with only doxycycline, we decided not to perform a biopsy.

## Discussion

Secondary nephrotic syndrome can be caused by various factors, including collagen diseases such as systemic lupus erythematosus and

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IgA vasculitis, and infectious diseases such as streptococcal infection, hepatitis B and C, HIV, and syphilis. Nephrotic syndrome is a well-known complication of syphilis, and an older study from 1935 has reported an incidence of 0.28 % [10].

In our case, the patient had rosacea and fever, suggesting the development of nephrotic syndrome associated with secondary syphilis. Since the treatment of syphilis with doxycycline alone resulted in the improvement of proteinuria and clinical symptoms, a clinical diagnosis of nephrotic syndrome due to syphilis was made. Furthermore, nephrotic syndrome caused by syphilis can be complicated by hepatitis and neurosyphilis; however, in this case, there was no liver injury, and cerebrospinal fluid showed no evidence of meningitis. Therefore, we did not consider central nervous system penetration and treated it as secondary syphilis. In addition, in this case, renal biopsy was not performed because proteinuria was treated with antibiotics only. Generally, in most cases of nephrotic syndrome caused by syphilis, renal pathology shows a form of membranous nephropathy [3], [4]. Secondary nephrotic syndrome due to syphilis is a well-known but rare complication, and the incidence of nephrotic syndrome in early syphilis was reported to be 0.28 % in an older study in 1935 [9]. Therefore, we performed a literature review to determine the current incidence of syphilis-associated nephrotic syndrome as well as other complications and patient characteristics.

We conducted English-language and Japanese-language literature reviews of secondary nephrotic syndrome related to syphilis. Data on patient demographics, clinical characteristics, HIV status, biopsy information, management, and outcomes were collected and are summarized in Table 1. Two authors (K.S. and K.I.) independently reviewed the titles and abstracts from database records, retrieved full texts for eligibility assessment, and extracted data from these cases. We performed a search using the keywords “syphilis” and “nephrotic syndrome” in PubMed, EMBASE, and Ichushi electronic databases from their inception to June 10, 2022, yielding 382 articles. The search formula is as follows: PubMed; ("Syphilis"[MeSH Terms] OR "syphili*"[Text Word]) AND ("nephrotic syndrome*"[Text Word] OR "Nephrosis"[MeSH Terms] OR "Nephrosis"[Text Word] OR "Nephroses"[Text Word] OR "glomerulonephritis"[Text Word] OR "nephropath*"[Text Word] OR "Kidney Diseases"[MeSH Terms]), Embase; (('syphilis'/exp OR 'syphilis') AND ('kidney disease'/exp OR nephrotic OR nephros* OR 'glomerulonephritis' OR nephropath*)) NOT (('syphilis'/exp OR 'syphilis') AND ('kidney disease'/exp OR nephrotic OR nephros* OR 'glomerulonephritis' OR nephropath*) AND ([medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)), Ichushi; ((Nephro/AL) or ([Kidney Disease]/TH)) and ((Syphilis/TH or syphilis/AL)) [Search words are in Japanese]. After screening all the articles and excluding those that were not case reports or did not report on syphilis and nephrotic syndrome, 132 case reports describing 150 cases of syphilis and nephrotic syndrome remained (Supplementary Table). Our literature review revealed that the most common pathology was membranous nephropathy, as in previous studies [3], [4].

Syphilis can facilitate the transmission of HIV, and there is a high rate of HIV coinfection in patients with syphilis among men who have sex with men. In our literature review, HIV infection was observed in 19 cases (12.7 %) of syphilis. Generally, neurosyphilis is observed more frequently in patients with HIV infection than in those without [5–8], and more attention should be paid to neurosyphilis and central gumma in these cases.

The literature review further revealed that the remission rate was as high as 76 %, and most cases that required dialysis and led to death occurred before the year 1950. The mortality rate before 1950 was 22.2 %, while the mortality and dialysis rate after 1950 was 4.3 %. Many of the cases of syphilitic nephrotic syndrome in the modern era have gone into remission. Compared with idiopathic nephrotic syndrome, syphilitic nephrotic syndrome has a relatively better prognosis [9]; therefore, our findings suggest that if the cause of nephrotic syndrome is syphilis, antimicrobial therapy can be administered prior to treatment without necessarily performing a biopsy.

**Table 1**
Summary of complications, human immunodeficiency virus (HIV) status, pathology, and outcome.

| | n | % |
|---|---|---|
| Total | 150 | |
| Complications | | |
| Neurosyphilis | 11 | |
| Hepatitis | 18 | |
| Lung lesion | 2 | |
| Cholangitis | 1 | |
| Enterocolitis | 1 | |
| Gastric ulcer | 4 | |
| Liver mass | 1 | |
| Proctitis | 1 | |
| Rhabdomyolysis | 1 | |
| HIV positive | 19 | 12.7 |
| Pathology | 90 | |
| MN | 74 | 82.2 |
| MC | 5 | 5.6 |
| FSGS | 3 | 3.3 |
| MPGN | 2 | 2.2 |
| crescent | 5 | 5.6 |
| necrotizing CGN with greater than 75 % cellular crescents and MN | 1 | 1.1 |
| Cure rate | | |
| Improved | 113 | 76 |
| Hemodialysis | 4 | 2 |
| Death | 4 | 2.7 |
| No data | 29 | 19.3 |

Abbreviations: MN, membranous nephritis; MC, minimal change; FSGS, focal segmental glomerular sclerosis; MPGN, membranoproliferative glomerulonephritis; CGN, chronic glomerulonephritis

## Conclusions

We report a case of syphilitic nephrotic syndrome that went into remission after syphilis treatment alone. Although a renal biopsy was not performed, most patients have been reported to have membranous nephropathy, with a good outcome following the use of antibacterial agents alone, as in this case. With the rapid increase in the incidence of syphilis, it is important to recognize that various symptoms can occur.

## Ethical approval statement

Not applicable. Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent form is available.

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## CRediT authorship contribution statement

**Nobuyoshi Mori:** Writing – review & editing. **Fujimi Kawai:** Data curation. **Kazuhiro Ishikawa:** Data curation. **Koko Shibutani:** Data curation, Formal analysis, Investigation, Writing – original draft.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

*Author Agreement Statement*

We the undersigned declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that all have approved the order of authors listed in the manuscript us.

We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions, and final approval of proofs.

*Authors' contributions*

All the authors contributed to this report. K.S. and K.I. collected clinical data and wrote the initial draft of the manuscript. KS, KI, and FK reviewed the literature. NM supervised and edited the manuscript. All authors read and approved the final draft of the manuscript.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.idcr.2024.e02016.

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