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CASE REPORT | LIVER

# Secondary Syphilis Can Simultaneously Mimic Cholestatic Liver Injury and Glomerular Nephropathy

Rachel Obimah, MD[1], Omar Martinez-Uribe, MD[2], James Helzberg, MD[2], Jane P. Gagliardi, MD, MHS[1], and Matthew Kappus, MD[2]

[1]*Department of Medicine, Duke University School of Medicine, Duke University, Durham, NC*
[2]*Department of Medicine, Division of Gastroenterology, Duke University School of Medicine, Duke University, Durham, NC*

## ABSTRACT

Syphilis, a disease affecting millions, still poses challenges for men who have sex with men in high-income countries and often presents in varying ways. It is exceedingly rare for syphilis to simultaneously cause an acute liver injury and nephropathy. This case describes the concomitant clinical presentation of these abnormalities and also describes a liver injury that mimicked cholestatic disease. Treatment of syphilis led to complete resolution of the liver and kidney injury. This case demonstrates a need to exclude syphilis in patients with high-risk behaviors who present with cholestatic liver injury in atypical fashions.

**KEYWORDS:** syphilis; hepatitis; nephropathy; primary biliary cholangitis

## INTRODUCTION

Syphilis is a global disease that affects over 50 million people worldwide[1] and remains a significant challenge for men who have sex with men (MSM) in high-income countries.[2] In the United States, there has been a marked increase in the incidence of syphilis overall.[3] With a variety of manifestations that often mimic other illnesses, syphilis is sometimes called "the Great Mimicker."[4] Although rare, several reports exist of secondary and tertiary syphilis causing syphilitic hepatitis.[5] Fewer reports exist of syphilis causing renal disease such as nephrotic syndrome.[6] Concomitant clinical presentation of syphilitic hepatitis with renal disease is exceedingly rare.[7] This case describes the simultaneous presentation of an acute nephropathy and cholestatic hepatitis secondary to syphilis infection in which the initial presentation was concerning for a cholestatic liver disease.

## CASE REPORT

The patient is a 29-year-old man with no significant medical history who presented to the emergency department with epigastric abdominal pain. He reported a 1-week history of tea-colored urine, pale stools, and diffuse pruritus that preceded a new rash. He denied taking any medications including over-the-counter herbal supplements or analgesics. He reported occasional alcohol consumption of about 2–3 standard drinks several days a month. His social history was relevant for identifying as MSM and reporting unprotected sex with multiple partners several months before symptom onset. Physical examination revealed a diffuse papular rash involving the palms, soles, trunk, face, and groin, as well as scleral icterus. His abdominal examination was without any notable hepatomegaly or tenderness to palpation. Laboratory results were significant for elevated alkaline phosphatase (279 U/L), aspartate aminotransferase, and alanine transaminase, 70 U/L and 167 U/L, respectively, with an elevated total bilirubin of 5.6 mg/dL (conjugated bilirubin of 3.7 mg/dL). Urinalysis revealed 3+ urine bilirubin and 4+ protein; serum creatinine was normal at 1.0 mg/dL. In addition, the random urine protein-to-creatinine ratio was elevated at 6,667 mg/g, with a 24-hour urine collection ultimately revealing 13.3 g protein. Serum albumin notably was low at 2.6 g/dL. A ferritin was not collected.

Five days before presentation, antimitochondrial antibody (AMA) and antismooth muscle antibody (ASMA) had been sent, and they returned positive (AMA 57 U, ASMA 31 U). Hepatitis screen was negative for acute hepatitis A, B, or C infection. Magnetic resonance cholangiopancreatography demonstrated moderate intrahepatic biliary dilatation and heterogeneous perfusion of the liver. Hepatology was consulted for further evaluation of primary liver pathology. They recommended further investigation of

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**Correspondence:** Rachel Obimah, MD (rachel.obimah@duke.edu).

systemic infectious or inflammatory etiologies and repeating AMA/ASMA serologies, given the acute onset nature of the patient's symptoms. Considering the patient's rash, the history of unprotected sex, and high-risk group (MSM), syphilis screening was performed. A diagnosis of secondary syphilis was made with rapid plasma reagin titer of 1:128 and confirmatory treponemal testing. Nephrology was not consulted for the proteinuria with what was felt to be a unifying diagnosis of secondary syphilis, with a plan to treat and monitor for improvement. The patient was administered a one-time dose of intramuscular penicillin G benzathine. At a 3-week follow-up appointment, there was a decrease in protein-to-creatinine ratio to 51 mg/g. By 7 weeks, there was complete resolution of his rash, pruritus, and tea-colored urine with normalization of his liver enzymes (Table 1). Of note, repeat AMA and ASMA were negative even before the treatment.

## DISCUSSION

A literature review describes syphilitic hepatitis as involving a cholestatic liver injury pattern but does not include any presentation with positive autoantibody testing.[8] Few cases describe syphilitic hepatitis presenting with a positive AMA, transiently elevated alkaline phosphatase, and mildly abnormal aspartate aminotransferase and alanine transaminase.[9] This patient presented with features mimicking primary biliary cholangitis (PBC) and glomerular nephropathy. In addition, the patient exhibited positive AMA and ASMA serologies, which subsequently returned negative before the initiation of secondary syphilis treatment. This observation suggests that his initial results were falsely positive due to a robust immune response.

On noting the simultaneous occurrence of cholestatic liver injury and nephropathy, a systemic etiology was strongly suspected. The focus of his care pivoted to finding a unifying cause rather than seeking further consultation with nephrology. The diagnosis of syphilis prompted literature review, which revealed cases of secondary syphilis causing glomerular nephropathy. The pathophysiology is poorly understood but believed to involve immune complex deposition within the glomeruli.[10] With a unifying diagnosis and plan for close follow-up, further investigation of alternative etiologies of his kidney disease was not completed; risk-benefit considerations led to the decision to not undergo kidney or liver biopsy during the hospitalization.

This case emphasizes the importance of recognizing anchoring bias that can often cause misdiagnosis and delay care. In clinical practice, anchoring bias is often a result of chart review that leads a clinician down a decision-making pathway before meeting the patient.[11] This patient presented to the team with medical records showing reports of cholestasis (ie, pruritus, scleral icterus, and pale stools), cholestatic liver injury, and a positive AMA. These features suggest a possibility of PBC, which was initially on the differential. PBC is a chronic autoimmune disease with a progressive course and is often diagnosed in women in their 5th or 6th decade of life.[12] Patients with PBC typically have a far more indolent course, usually with fatigue and pruritus and slow development of jaundice.[13] In this case, the patient presented with features atypical of PBC, such as a diffuse rash along the palms and soles, biliary dilatation, evidence of glomerular injury, and a sudden onset of symptoms. Because the patient's clinical presentation was atypical for PBC, nonjudgmental history-taking was used, and autoantibodies were retested. This encouraged consideration of a different, more unifying diagnosis as outlined in Figure 1. To mitigate anchoring bias, an emphasis is placed on the ability to identify atypical patterns and subsequently broaden the differential diagnosis accordingly.

**Table 1. Laboratory findings before and after treatment of secondary syphilis causing concurrent cholestatic hepatitis and glomerular nephropathy**

| | Value at presentation | 3 weeks post-treatment[a] | 7 weeks post-treatment[a] |
|---|---|---|---|
| Liver enzymes | | | |
| Aspartate aminotransferase U/L | 70 | 75 | 27 |
| Alanine transaminase U/L | 167 | 124 | 40 |
| Alkaline phosphatase U/L | 279 | 243 | 74 |
| Bilirubin, total mg/dL | 5.6 | 1.7 | 0.8 |
| Urine studies | | | |
| Urine analysis protein | 4+ | Trace | |
| Urine analysis bilirubin | 3+ | Negative | |
| Creatinine, random urine mg/dL | 220 | 234 | |
| Protein, random urine mg/dL | 1,466 | 12 | |
| Total protein/creatinine ratio mg/g | 6,667 | 51 | |

a Treatment included the administration of penicillin G benzathine 2.4 million units intramuscularly the day after presentation.

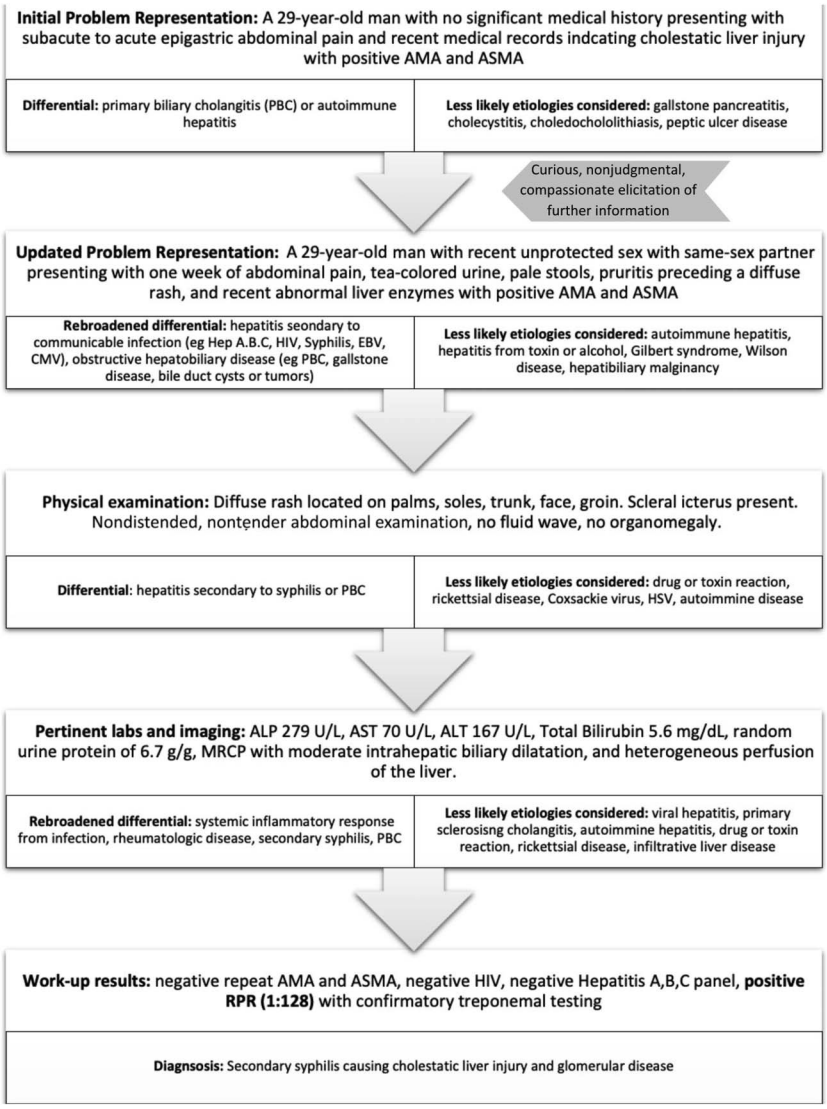


**Figure 1.** Clinical reasoning process during case presentation, demonstrating the requirement of thoughtful reconsideration and broadening of a differential diagnosis to avoid anchoring bias after atypical findings emerged. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ASMA, antismooth muscle antibody; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MRCP, magnetic resonance cholangiopancreatogrpahy; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; RPR, rapid plasma regain.

Syphilis is a global disease and has an increasing incidence in men who have sex with men. This case highlights the need to consider syphilis in high-risk groups, even in cases of cholestatic liver injury and nephrotic syndrome, to land on a more accurate and timely diagnoses. By recognizing atypical features in this patient's presentation, providers were able to elucidate a diagnosis of secondary syphilis, an etiology that is treatable if detected, and facilitate the patient's return to normal liver and kidney function.

## DISCLOSURES

Author contributions: All authors listed have made substantial contribution to the conception and design of this case report. This work was drafted by R. Obimah and O. Martinez-Uribe and critically reviewed for important intellectual content by J. Helzberg, J. Gagliardi, and M. Kappus. All authors listed have participated in the final approval of the version to be published and agree to be accountable for all aspects of the case report. M. Kappus serves as the supervising investigator and guarantor.

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