

The Great Imitator strikes again: a hepatobiliary puzzle unraveled by a skin biopsy

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Abstract

Hepatic syphilis is a rare and often overlooked cause of cholestatic liver injury. A 65-year-old male presented with new-onset cholestasis, severe pruritus, weight loss, and marked elevation of CA 19-9. MRCP revealed irregular ductal calibers in a PSC-like pattern with biliary dilatation predominantly on the right side with stricture of the central bile ducts with a central filling defect, initially raising concern for occult cholangiocarcinoma. Histology from cholangioscopic bile duct biopsies demonstrated nonspecific inflammation. Concurrent dermatologic evaluation of a persistent rash led to a punch biopsy showing plasma-cell-rich inflammation, prompting serologic testing that confirmed active syphilis. Spirochetes were visualized on bile duct tissue using specific staining. This case highlights the protean manifestations of *Treponema pallidum*, including its ability to mimic PSC and even malignancy. Clinicians should maintain a low threshold for syphilis testing in unexplained cholestasis, even in the absence of overt risk factors, to avoid misdiagnosis and delayed treatment. (*Acta gastroenterol belg.*, 2026, 89, 495-498).

Keywords: Syphilitic hepatitis, cholangiopathy, primary sclerosing cholangitis mimic, *Treponema pallidum*, cholangioscopy, cholestatic liver injury.

Introduction

Cholestatic liver diseases such as primary sclerosing cholangitis (PSC) are relatively rare but carry significant morbidity, often necessitating lifelong surveillance and treatment. By contrast, infectious causes of biliary injury may be reversible—but can be easily overlooked (1). Syphilis, caused by the intracellular Gram-negative spirochete *Treponema pallidum*, is well-known for its protean clinical manifestations. While syphilitic hepatitis has been described, its presentation as a cholangiopathy is less reported (2).

We report here a case of syphilitic involvement of the bile ducts into a PSC-mimic with initially concern for occult cholangiocarcinoma. In discussion the relevant literature is briefly discussed.

Case history

A 65-year-old man was referred urgent by his general practitioner for newly-onset cholestasis and weight loss. He reported a weight loss of six kilogram over a short period, severe pruritus, and skin excoriations with an underlying rash. He was in a fair general condition, with no known major comorbidities aside from compound heterozygous genotype for

haemochromatosis (with hyperferritinaemia) and a prior uncomplicated episode of diverticulitis. He had not been taking any newly started medications, was a non-smoker and consumed approximately four units of alcohol per week. He was married and had two children.

The initial laboratory findings demonstrated an alkaline phosphatase (AP) of 1083 U/L, a gamma-glutamyl transferase (GGT) of 680 U/L, a bilirubin of 1.57 mg/dL, an aspartate aminotransferase (AST) of 101 U/L, and an alanine aminotransferase (ALT) of 184 U/L.

There was a mild inflammatory response, with a C-reactive protein (CRP) level of 40 mg/L without leukocytosis.

Most concerning was a significantly elevated CA 19-9 of 9600 kU/L (reference < 37).

Viral serology revealed past Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infection, negative hepatitis B surface antigen with positive surface and core antibodies (consistent with past resolved HBV infection), and no evidence of prior or current hepatitis A or C infection.

Initial image evaluation with ultrasound and CT abdomen revealed mild diffuse intrahepatic bile duct dilatation without an identifiable cause. The pancreas appeared normal.

MRCP demonstrated diffuse intrahepatic bile duct dilatation, predominantly in the right hepatic lobe, with irregular bile duct calibers and skip lesions at multiple sites suggestive for PSC. A stricture of the central bile ducts with a central filling defect was observed on MRCP sequences (Figure 1). These findings were initially most suggestive of an underlying occult cholangiocarcinoma. PET-CT demonstrated a subtle heterogeneous hypermetabolism at the hepatic hilum, without additional abnormalities.

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Figure 1. — MRCP and occlusion cholangiography demonstrating multifocal biliary abnormalities.

Left: MRCP image demonstrating intrahepatic biliary dilatation predominantly on the right side, with a stricture of the central bile ducts and a central filling defect. Additional findings include skip lesions at multiple sites and irregular ductal calibres.

Right: Occlusion cholangiography showing a hilar stricture extending across both hepatic ducts.

Multidisciplinary discussion recommended further work-up with endoscopic ultrasound (EUS) and ERCP with cholangioscopy. EUS demonstrated discrete dilatation of the intrahepatic bile ducts and an enlarged lymph node measuring 16×10 mm adjacent to the common bile duct and portal vein, from which fine-needle biopsy was performed.

ERCP with occlusion cholangiography showed irregular bile duct calibers and diffuse sub-stenoses compatible with PSC, with a hilar stricture extending across both hepatic ducts (Figure 1).

Additional endoscopic cholangioscopy revealed a villous and inflamed mucosa at the biliary bifurcation, which can be consistent with sclerosing cholangitis. Snake-bite biopsies were taken. No lesion suspicious for malignancy was seen.

Cytology from the lymph node fine-needle biopsy was entirely benign. Histology from the cholangioscopic biopsies showed inflammatory changes only, without evidence of atypia or malignancy.

A tentative diagnosis of PSC was therefore made, and therapy with ursodeoxycholic acid was initiated with close follow-up of biochemical parameters and imaging studies. Subsequent follow-up showed moderate clinical and biochemical improvement but persistent cholestasis.

At the same time of hepatobiliary work-up, dermatological evaluation was initiated for the pruritic skin eruption, characterized by multiple excoriated papules scattered over the trunk and limbs. Initial treatment with topical corticosteroids was prescribed. Due to persistence of the lesions after several weeks, a punch biopsy was subsequently obtained from the back.

This showed superficial and deep lymphoid inflammation with numerous plasma cells. The pathologist suggested that while an autoimmune etiology could not be excluded, infectious origin (e.g., spirochetes) should

be considered. This finding prompted serologic testing for spirochetes, which ultimately confirmed an active syphilis infection (TPHA $> 1:10240$, RPR (VDRL) 1:128). HIV testing was negative.

The pathologist was asked to perform additional spirochete stains on the bile-duct biopsies, which revealed numerous spirochetes (Figure 2).

The patient had concealed a history of extramarital affairs for years and did not disclose it during consultation. He was treated with intramuscular benzylpenicillin, 2.4 million IU for three weeks. On follow-up skin eruption and pruritus resolved, body weight stabilized, cholestatic enzymes progressively declined and CA 19-9 level normalized. MRCP at latest review still shows features consistent with a PSC-type residual pattern, which is likely sequelae rather than ongoing active disease. Mild residual cholestasis (GGT 97 U/L – AP 151 U/L) persists biochemically. The patient remains under follow-up.

Discussion and literature review

This case highlights an unusual presentation of *Treponema pallidum* infection manifesting as a PSC-like cholangiopathy, with even an initial suspicion of an underlying occult cholangiocarcinoma on imaging.

While hepatic involvement in primarily secondary syphilis has been recognized for more than a century, its presentation as sclerosing cholangitis remains rare. The pathophysiology is thought to involve direct biliary tract infiltration, resulting in a cholestatic enzyme pattern and biliary irregularities on imaging (2).

Wallace et al. (2015) published the first case report describing a PSC-like pattern in syphilitic hepatitis with clear abnormalities on MRCP (3). This case revealed a pathophysiological component that had likely remained underrecognized in the past due to limited use or

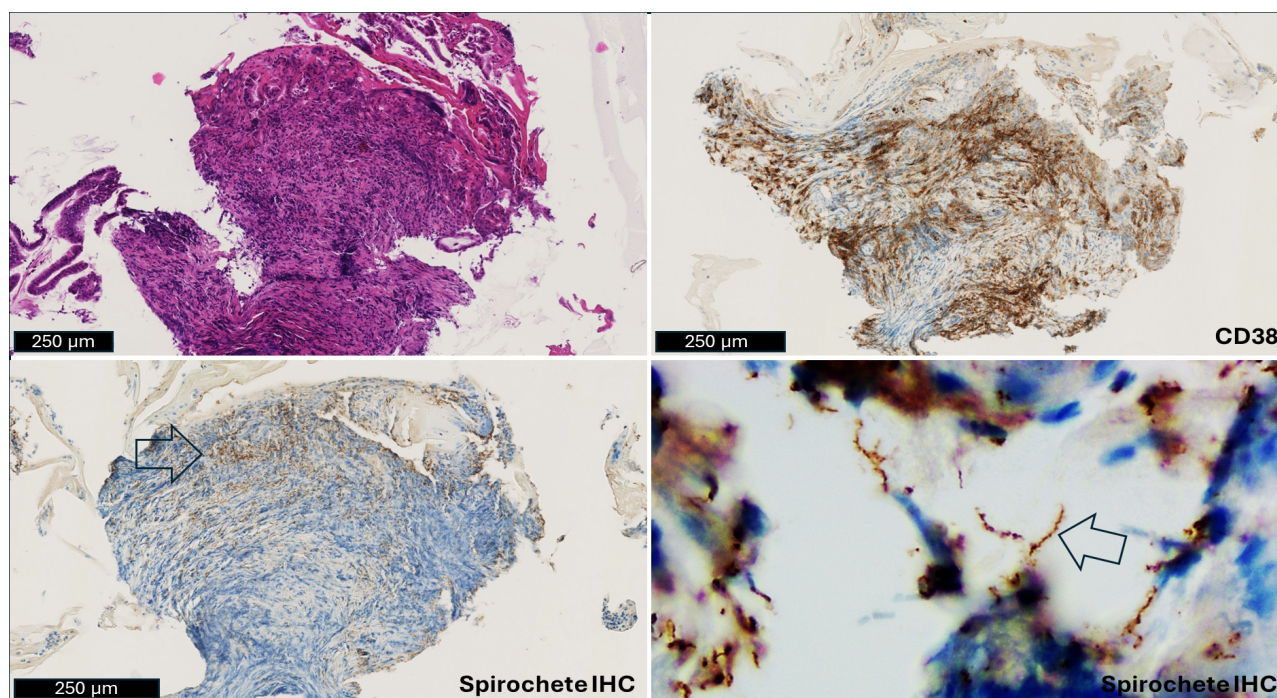


Figure 2. — Immunohistochemical identification of *Treponema pallidum* in bile-duct biopsy with plasma-cell-rich Inflammation.
 Upper left: Fragment from a cholangioscopic biopsy reveals fibrous tissue containing numerous crushed inflammatory cells, suggestive of lymphocytes. No evidence of malignancy is observed. Hematoxylin and eosin (H&E) stain.
 Upper right: CD38 immunohistochemistry demonstrates that the crushed inflammatory infiltrate includes numerous plasma cells, which are not identifiable on the H&E stain.
 Lower left: Immunohistochemical stain for spirochetes showing numerous positively stained organisms (open arrow).
 Lower right: Higher magnification (1000 $\times$, oil immersion) highlighting the characteristic curved morphology of *Treponema pallidum* (syphilis organisms).

lower resolution of MRCP imaging. In the systematic review by Huang et al., encompassing 144 adult cases of syphilitic hepatitis, over three-quarters presented with rash and cholestatic liver enzyme elevations characterized by a marked rise in alkaline phosphatase (mean 684.5 U/L) in contrast to mild transaminase elevations, further supporting the biliary component in the pathogenesis of syphilitic liver involvement (4).

Histopathological changes of syphilitic hepatobiliary involvement are nonspecific and variable, most commonly showing portal and lobular inflammatory infiltrates, ductular reaction, and, in some instances, granulomatous reactions (5). Because spirochete staining is not routinely performed, specific testing—by immunohistochemistry or Warthin–Starry technique—must be explicitly requested. Nevertheless, direct visualization of spirochetes is not guaranteed in liver biopsies, illustrated in two publications, in which 10 of 14 and 19 of 28 biopsies yielded a positive result, with the majority detected by immunohistochemistry (4, 5). Uniquely, in our case, bile duct biopsies obtained during endoscopic cholangioscopy demonstrated spirochetes directly, representing, to our knowledge, the first such report in the literature. This finding raises the hypothesis that endoscopically obtained bile duct biopsies may offer a higher diagnostic yield than conventional liver biopsies, given the organism's preferential intra- and periductal localization. Nevertheless, histopathological

confirmation is by no means required for the diagnosis, as no pathognomonic pattern has been established. Likewise, failure to demonstrate spirochetes in tissue specimens does not rule out the diagnosis.

The diagnosis of syphilis relies primarily on the clinical presentation—often including a characteristic rash—in combination with positive serologic testing, using both non-treponemal assays (RPR - VDRL) and treponemal tests (TPHA). They exhibit high specificity and a sensitivity approaching 100% in the secondary stage of syphilis(6). Therefore, they provide a simple and reliable means to consider or rule out syphilis in the differential diagnosis of unexplained hepatic dysfunction.

Interestingly, syphilis has also been reported to mimic primary biliary cholangitis (PBC), as false-positive reactions to the PBC-specific anti-M2 AMA antibodies have been described, which normalized after appropriate treatment (7). An illustration of immunologic cross-reactivity that underscores the protean behavior of *Treponema pallidum* and the ongoing necessity for diagnostic caution.

To date, standardized diagnostic criteria for syphilitic hepatitis have not been established. Mullick et al. (2004) proposed a practical framework based on four defining features to support the diagnosis: (i) abnormal liver enzyme levels; (ii) serological evidence for syphilis; (iii) exclusion of other liver diseases; and (iv) normalization

of liver enzymes following antibiotic therapy (8). Our case meets all four criteria, demonstrating that this framework is versatile and comprehensive enough to capture the great imitator, syphilis, and should be advocated for continued application.

The treatment of syphilis is straightforward, consisting of penicillin, and in most cases results in rapid and complete normalization of liver function tests (9). The imaging abnormalities on MRCP also demonstrate almost complete resolution (2, 3). In our case, the MR abnormalities persisted at follow-up, presumed to be residual fibrotic changes despite microbiological cure. However, imaging was performed within two months after treatment, leaving open the possibility that further normalization may occur over a longer period. Continued radiologic follow-up has been planned.

Given the ongoing global resurgence of syphilis, clinicians should be aware that *T. pallidum* can masquerade as autoimmune or malignant hepatobiliary disease (10). A broad differential—especially in the presence of rash, unexplained cholestasis, and high alkaline phosphatase - should include syphilis, even when social history appears low-risk. Early serologic testing and multidisciplinary assessment (hepatology, dermatology, pathology) are critical to prevent long-term misdiagnosis and unnecessary invasive interventions.

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