中文題目：案例報告---梅毒感染誘發的膽汁鬱積以及高膽固醇血症

英文題目：**A case of syphilis presenting with cholestasis and hypercholesterolemia**

作　　者：曾逸宏[1]、李淳權[1]、徐嵩庭[2]

服務單位：[1]馬偕醫院內分泌暨新陳代謝科、[2]馬偕醫學院醫學系

Abstract

In this report, we describe a 37-year-old man who initially presented with jaundice. During hospitalization, an acute liver injury [aspartate aminotransferase (AST): 203 IU/L; alanine aminotransferase (ALT):621 IU/L] with hyperbilirubinemia (total bilirubin: 11.5 mg/dL) and hyperglycemia (blood glucose: 388 mg/dL) was noted. HIV antigen/antibody (Ag/Ab) combo, hepatitis B virus soluble antigen (HBsAg), anti-hepatitis A virus (HAV) IgM and hepatitis C virus (HCV) Ab tests were non-reactive. Abdominal sonography revealed a fatty liver without common bile duct dilatation. However, a rapid plasma reagin test and treponemal test were positive (1:128 titer and signal-to-cutoff ratio of 20.72, respectively). The patient had strikingly high total cholesterol and low-density lipoprotein cholesterol (LDL) levels (1670 and 1506 mg/dL, respectively). We arranged plasma exchange after discussing the advantages and disadvantages with the patient. After 3 consecutive days of plasma exchange and benzathine penicillin treatment, his cholesterol and bilirubin levels declined dramatically. These levels remained stable during follow-up. We reported this case to discuss the relationship between syphilis, jaundice and hypercholesterolemia. We will also discuss issues affecting the treatment of cholestasis-related hypercholesterolemia.

Key words: syphilis, jaundice and hypercholesterolemia

Case report

A 37-year-old man presented with jaundice accompanied by tea-colored urine for a 1-week duration and generalized weakness and skin pruritus for a 1-month duration. He had lost approximately 2–3 kilograms during the previous 3 months. He denied febrility, abdominal pain, nausea, vomiting or taking drugs. He exhibited the following vital signs upon arrival at our emergency room: temperature, 37 ºC; pulse rate, 97 beats per minute; respiratory rate, 18 breaths per minute and blood pressure, 131/72 mmHg. A physical exam revealed icteric sclera, multiple pigmented and poorly healing scars on his limbs and multiple non-pruritic desquamated papules on the bilateral soles of his feet. He reported that these papules had developed during the previous 3 weeks. The physical examination also revealed mild localized tenderness in the right abdomen. He further reported a history of sexual contact with men who have sex with men (MSM) without using a condom during four events in the previous year.

The initial laboratory analysis yielded the following data: total bilirubin: 9.3 mg/dl(0.3–1.2 mg/dL , normal reference values were listed in the following parentheses); direct bilirubin: 5.8 mg/dl (0.1–0.5 mg/dL); AST: 203 IU/L (15–41 IU/L); ALT: 621 IU/L (14–40 IU/L); alkaline phosphatase: 1021 IU/L (38–126 IU/L) and gamma-glutamyl transferase: 1487 IU/L (7.0–50 IU/L). The following blood lipid values were obtained: total cholesterol, 1670 mg/dL; LDL: 1506 mg/dl; high-density lipoprotein cholesterol (HDL): 51 mg/dL and triglyceride, 514 mg/dL. Another biochemical examination revealed the following: 309 mg/dL; glycated hemoglobin (HbA1c): 12.6%; blood urea nitrogen (BUN): 16 mg/dL (8–20 mg/dL), creatinine: 0.9 mg/dL (0.4–1.2 mg/dL); potassium: 4.0 meq/L (2.5–5.1 meq/L); sodium: 124 meq/L (136–144 meq/L) and alpha-fetoprotein: 1.05 ng/mL (<10.00 ng/mL). HIV Ag/Ab combo, HBsAg, anti-HAV IgM and HCV Ab tests were all non-reactive. However, positive RPR (titer: 1:128) and treponemal test results (signal-to-cutoff ratio: 20.72) led to a diagnosis of syphilis.

Abdominal sonography revealed a fatty liver without common bile duct dilatation. An abdominal computed tomography scan reported neither an obvious parenchymal lesion nor grossly enlarged lymph nodes and no abnormal dilatation of the intrahepatic and extrahepatic bile ducts, gallbladder or main pancreatic duct.

The patient had no significant family history of hyperlipidemia or vascular disease. He reported no personal or family history of tendon xanthomas. A thyroid function test and urinary analysis were performed to rule out secondary causes such as hypothyroidism or

nephrotic syndrome. The thyroid analysis revealed the following: thyroid-stimulating hormone, 1.19 μIU/mL (0.25–4.00 μIU/mL) and free-T4, 1.25 ng/dL (0.89–1.79 ng/dL). Urinary analysis revealed the following: creatinine: 49.7 mg/dL; microalbumin (urine): <0.5 mg/dL (<1.9 mg/dL); microalbumin/creatinine ratio <10.1 % (<30.0%). These results suggested neither hypothyroidism nor nephrotic syndrome.

We prescribed benzathine penicillin G (*intramuscular injection of 2.4 million units weekly for 3 consecutive weeks*) for syphilis. We also discussed the advantages and disadvantages of using apheresis or plasma exchange to treat his strikingly high cholesterol levels. He agreed to undergo plasma exchange. After the first dose of benzathine penicillin G and 3 consecutive days of plasma exchange, his total cholesterol, total bilirubin, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) level declined to normal limits within a week (Figures 1 and 2). His cholesterol and bilirubin levels then remained stable at his 2- and 5-month follow-ups (Figure 1 and 2).

Discussion

The clinical manifestations of syphilis are mostly associated with a wide variety of mucocutaneous manifestations. However, syphilis can also manifest with hepatic involvement. Up to 25% of patients may receive abnormal liver function test results, although most are asymptomatic.[1] A review of cases of syphilitic hepatitis demonstrates striking increases in alkaline phosphatase and gamma-glutamyl transferase levels and minor to moderate increases in aminotransferase levels.[2-6] In these cases, the alkaline phosphatase, gamma-glutamyl transferase, bilirubin, GOT and GPT levels returned to normal limits within weeks to months after treatment with injected antibiotics.[7,8] Additionally, common mucocutaneous signs may be absent in cholestasis and jaundice secondary to syphilis.[6] Therefore, it may be difficult to reach a diagnosis of syphilis. Liver biopsy usually reveals changes such as portal inflammatory infiltration, hepatocellular necrosis, Kupffer cell hyperplasia, granulomas and, in some cases, spirochetes.[2,5-7] In our case, the patient's biochemical profile improved quickly and remained stable within normal limits following treatment with injected antibiotics and plasma exchange. The absence of a hepatitis virus and history of alcoholism and the rapid response to penicillin strongly suggests a link between cholestasis hepatitis and syphilis. We report this case to emphasize that syphilis may be included as a differential diagnosis in a case of undiagnosed hepatic disease, even if the patient does not present with typical mucocutaneous signs.

We further reviewed articles describing the progression from obstructive liver disease to hypercholesterolemia. We searched the PubMed database using the MeSH terms "Hypercholesterolemia" and "Cholestasis." Most available articles discussed primary biliary cirrhosis (PBC) and related hypercholesterolemia.[9-15] Here, the serum cholesterol level may increase as cholestasis progresses or PBC worsens.[12] Hypercholesterolemia is often linked to an increased risk of cardiovascular disease.[16] Some reports did not observe an association of hypercholesterolemia in PBC with an increasing risk of cardiovascular disease.[9,10,12]However, a 2006 systemic review posted in *Atherosclerosis* 2007;194(2):293-299 suggested that more research and additional data are needed to confirm whether hypercholesterolemia in PBC would increase the risk of cardiovascular disease.[14]

Abnormal lipoprotein X (Lp-X) is usually detected in patients with cholestasis-associated hypercholesterolemia.[16] Lp-X is associated with a deficiency in the cholesterol esterifying enzyme (LCAT) and impaired bile secretion, although the underlying mechanism is not fully understood.[16,17] As Lp-X is characterized by a low concentration of apo B-100, most hospital

lipid profile examinations cannot discriminate it from LDL.[18] This similarity might explain why the association between cardiovascular events and hypercholesterolemia consequent to obstructive liver disease less apparent than in cases of general hypercholesterolemia. The treatment of hypercholesterolemia due to cholestasis has been obscure.[14]Some research suggests that statins, which reduce primary bile acid production by reducing cholesterol synthesis, could be used to treat PBC.[19,20] However, it may be risky to prescribing statin drugs to patients with cholestasis not only because of the potential side effects, but also because of the potentially minimal effectiveness of the drugs.[21] More research, such as a randomized control trial, is needed to optimize the treatment of hypercholesterolemia in patients with cholestasis.

Acknowledgement

We acknowledge the efforts of all physicians and paramedics that assisted with this case.

Conflict of interest

The authors declare no potential conflicts of interest related to this case.

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Figure Legends

Figure 1: Graphic illustration of total bilirubin (mg/dl) and glutamic-pyruvate transaminase (IU/l) levels over time. Benzathine penicillin G administration (needle icon) and plasma exchange were done as shown in the graphic.

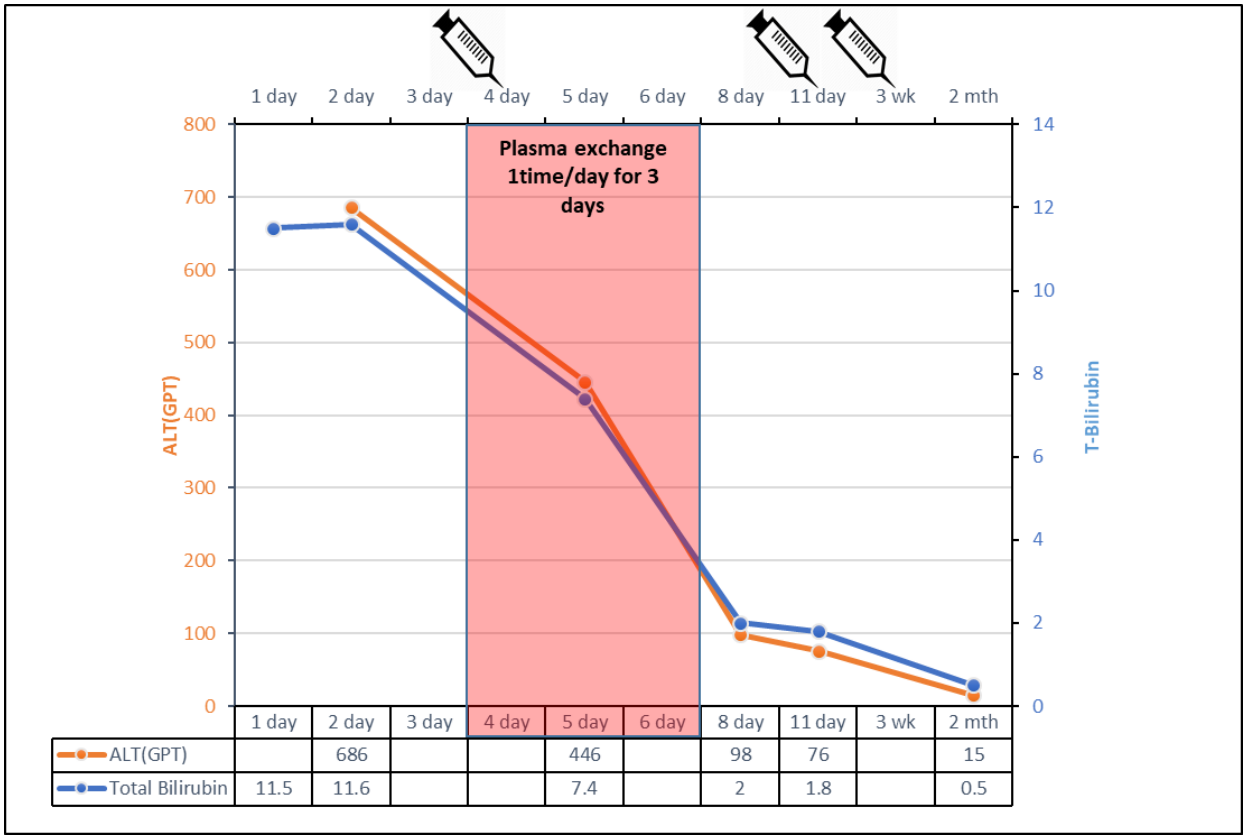
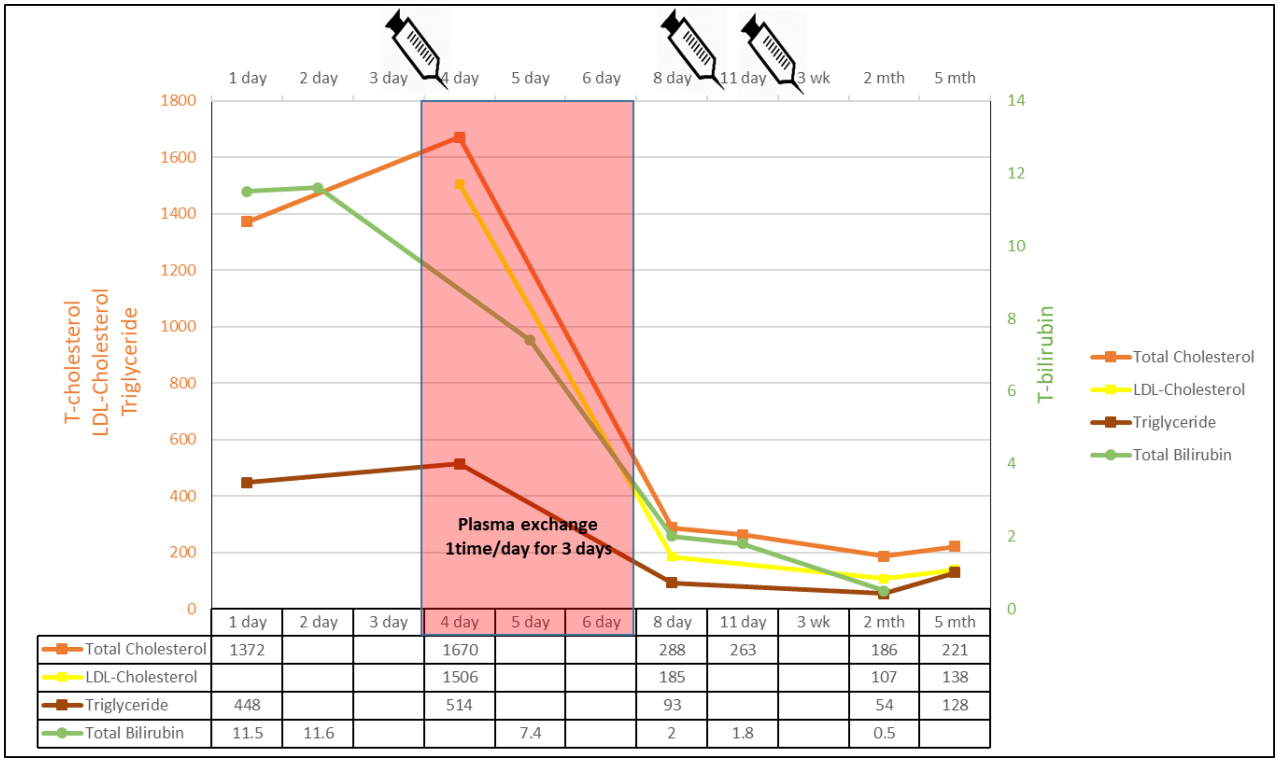


Figure 2: Graphic illustration of total cholesterol (mg/dl), low-density lipoprotein cholesterol (LDL; mg/dl) and triglyceride (mg/dl) levels over time. Benzathine penicillin G administration (needle icon) and plasma exchange were done as shown in the graphic.



	1 day	2 day	3 day	4 day	5 day	6 day	8 day	11 day	3 wk	2 mth	5 mth
Total Cholesterol	1372			1670			288	263		186	221
LDL-Cholesterol				1506			185			107	138
Triglyceride	448			514			93			54	128
Total Bilirubin	11.5	11.6			7.4		2	1.8		0.5	