1 Title

2 A case of secondary syphilis presenting with unusual complications: syphilitic proctitis,

3 gastritis and hepatitis
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We report the first known case of syphilis with simultaneous manifestations of proctitis, gastritis and hepatitis. The diagnosis of syphilitic proctitis and gastritis were established by the demonstration of spirochetes with anti-*Treponema pallidum* antibody staining in biopsy specimens. Unusual manifestations of secondary syphilis completely resolved after 4-week of antibiotic therapy.
Case report

A 28-year-old homosexual Japanese man was referred to our hospital for assessment of abnormal liver function test and circumferential thickening of the rectal wall. The patient presented with a 1-month history of diarrhea, painful defecation, occasional hematochezia and 1-week history of mild upper abdominal discomfort. He had been diagnosed as secondary syphilis in a local clinic a week prior to admission based on the serological test for syphilis (STS), *Treponema pallidum* hemaggulutination test (TPHA) and the classical skin lesion. The human immunodeficiency virus type 1 (HIV-1) screening test was negative.

Initial laboratory findings were as follows: white blood cell (WBC) count, 7,300 /µL (normal value, 3,900-9,800); red blood cell (RBC) count, 473×10⁴ /µL (410-530×10⁴); hemoglobin (Hb), 13.8 g/dL (13.5-17.6); platelet count (Plate), 29.5×10⁴ /dL (12-36×10⁴); total serumprotein (TP), 7.6 g/dL (6.5-8.0); aminotransferase (AST), 62 IU/L (8-38); alanine aminotransferase (ALT), 74 IU/L (4-44); lactate dehydrogenase (LDH), 175 mg/dL (115-224); alkaline phosphatase (ALP), 486 IU/L (104-338); γ-glutamyltranspeptidase (γ-GTP), 62 IU/L (16-73); fasting blood glucose (FBG), 84 mg/dL (70-107); serological test for syphilis (STS) (latex agglutination assay), 155.94 SU/ml; *Treponema pallidum* hemaggulutination test (TPHA) 1814.50 SU/ml.
On admission, body temperature was 37.8°C. The general physical examination was basically normal except for the bilateral inguinal lymphadenopathy without pain and presented the small, nonconfluent, erythematous, macular lesions on the trunk, back, arms and face. The patient admitted to recent unprotected, receptive anal intercourse. There were no detectable anal lesions but rectal examination showed circumferential thickening of the rectal wall. The colonoscopy showed an indurated nodular mucosa around the rectal lumen, which initially suggested a submucosal tumor. Barium enema showed the similar findings (FIG. 1A and B). Histologic findings of rectal mucosa revealed severe inflammatory cell infiltration predominantly by plasma cells. No malignant cells were identified. An immunostaining with anti-\textit{Treponema pallidum} polyclonal antibodies of rectal biopsy specimens identified numerous spirochetes and the diagnosis of syphilitic proctitis was confirmed.

He had been complaining of upper abdomen discomfort. His antecedent medical records including stomach disease were not remarkable. The gastroduodenoscopy showed multiple erosive lesions in whole gastric mucosa and numerous spirochetes were identified on an immunostaining of the biopsies specimens (FIG. 2A and B). Histologic examination of the mucosa shows mild infiltration of neutrophils with superficial necrosis and fibropurulent
exudates. There was no evidence of carcinoma, lymphoma or Helicobacter pylori infection.

Liver function test at admission showed elevated AST, 480 U/L; ALT 607 U/L; ALP, 2493 U/L; LDH 420 U/L; \(\gamma\)-GTP, 774 U/L and TB 1.1 mg/dl (0.1-1.0). Acute viral hepatitis was initially suspected, but serologic markers of acute viral infection shown below were all negative: IgM anti-hepatitis A virus (IgM-HAV), Hepatitis B virus (HBV) surface antigen (HBsAg), IgM anti-HBV core antigen (IgM-HBc), hepatitis C virus antibodies (HCV-Ab), IgM anti-hepatitis E virus (IgM-HEV), IgM anti-cytomegalovirus (IgM-CMV), IgM anti-viral capsid antigen of Epstein-Barr Virus (IgM-VCA EBV). On other hand, IgG-CMV, IgG-VCA EBV and EBV nuclear antigen (EBNA) were all positive, suggesting that he was previously infected with CMV and EBV. HBV-DNA, HCV-RNA and HIV-RNA were not detected. Both anti-mitochondrial M2 antibody and anti-smooth muscle antibodies were negative. Immunoglobulins, including IgE, were all normal. Antinuclear antibody (ANA) was positive at 1:40 (speckled pattern). However, autoimmune hepatitis was ruled out by other laboratory data and did not fulfill the criteria proposed by the international autoimmune hepatitis group. (9) The abdominal ultrasonography showed did not reveal any evidence of chronic liver diseases. There was no history of alcohol abuse, intravenous drug abuse, oral illicit drug use or smoking. The levels of ALP, \(\gamma\)-GTP and TB were
progressively elevated to, 5358 U/L, 1103 U/L and 1.9 mg/dl, respectively, 4 days after the admission. Liver biopsy was not done because the patient’s consent was not obtained. Although the etiology of liver enzyme abnormalities remained unclear, alternative causes of hepatic damage were excluded and syphilitic hepatitis was strongly suspected. There were no cerebrospinal fluid (CSF) abnormalities, including the level of STS and TPHA. Oral administration with 2.25 g/day amoxicillin hydrate (AMPC) was initiated according to the guideline proposed by The Japanese Society for Sexually Transmitted Disease. Jarisch-Herxheimer reaction, consisting of fever and skin rash deterioration, developed six hours after the first oral administration of AMPC but resolved spontaneously in 24 hours. Subsequent to the therapy, the liver function tests improved gradually and became normal after 4-week AMPC administration. Fever resolved promptly and skin lesions disappeared in a few days. Circumferential thickening of the rectal wall and upper abdominal discomfort were completely resolved together with the decrease in the level of STS to 5.28 SU/ml 2-month after the initiation of AMPC.

Treponema pallidum (*T. pallidum*), the etiologic agent of syphilis, is known to affect a wide variety of organs. Involvements of skin, genital organ, retina and central nervous
system are well described, but occasionally unusual manifestations can occur, such as gastrointestinal lesions, liver and renal dysfunction. We highlight here, *T. pallidum* as an important but often unrecognized agent that could involve rectum, stomach and liver simultaneously. In a search of the MEDLINE database since 1960, this is the first case report which manifested three unusual complications; proctitis, gastritis and hepatitis in secondary syphilis. Syphilitic proctitis is rarely reported but being recognized more frequently due to the increased incidence of syphilis among MSM recently. A retrospective review of clinical proctitis in MSM showed syphilis was found in 2% of clinical patients presenting with rectal symptoms (6). Anorectal primary syphilis is easily overlooked because of the absence of anal lesions in some cases. In addition, it is difficult to diagnose because clinical manifestations of syphilitic proctitis have been shown to mimic amoebiasis, Crohn’s disease, malignant lymphoma or carcinoma (4). Syphilitic gastritis is found in less than 1% of patients with syphilis and seldom reported (4). The gastroduodenoscopy features described in previous case reports are multiple erosive or ulcerative lesions in the whole gastric mucosa. Endoscopic and microscopic findings can mimic gastric cancer or lymphoma (7). To make a definitive diagnosis of syphilitic gastritis and proctitis, it is necessary to identify *T. pallidum* histologically. To
detect *T. pallidum* in tissue, immunohistochemistry staining with anti-*T. pallidum* polyclonal antibodies can be used as was in the present case. Recently, a better sensitivity and rapid diagnosis of gastric syphilis were achieved by using the real-time PCR (3).

Hepatitis, as well as proctitis and gastritis, are rare complications of syphilis. Liver dysfunction occurring in early syphilis has a diagnostic challenge. Clinical manifestations of syphilitic hepatitis described in previous reports showed that alkaline phosphatase was disproportionately elevated relative to bilirubin and transaminases (2). These features are consistent with our case. Mullick et al proposed the following criteria for the diagnosis of acute syphilitic hepatitis (10): abnormal liver enzyme levels indicating hepatic involvement; serological evidence for syphilis with a positive TPHA titer in conjunction with an acute clinical presentation consistent with secondary syphilis; exclusion of alternative causes of hepatic injury; and improvements in liver enzyme levels with an appropriate antimicrobial therapy. Our case met all of these criteria and we, therefore, attributed this patient’s liver dysfunction to the involvement of *T. pallidum* even though liver biopsy was not performed. Comparing with the gastrointestinal tissue, liver biopsy is likely to have lower yield to detect *T. pallidum*. The majority of reported cases since 1975 failed to reveal treponemes in liver biopsy specimens (1, 2, 8, 11). Although the precise
mechanism of involving three different organs in this case remains unclear, we believe that
the relationship between proctitis and hepatitis is related to the venous drainage pathway
from rectal area into the portal system. This postulation is supported by the fact that
syphilitic hepatitis occurs often in conjunction with syphilitic proctitis (5) and is seen
frequently in persons who engage in anal intercourse (2).

Syphilitic involvement for stomach, rectum and liver is easily overlooked and has not
been described in the modern literature to our knowledge. These are all reversible
conditions and appropriate antibiotic treatment results in rapid resolution. Therefore, the
diagnosis of these complications is important to prevent progression to a severe condition
and avoid unnecessary investigations. The clinicians should bear in mind the possibility of
syphilitic involvement in patients at risks for sexually transmitted diseases, who present
with either gastrointestinal discomfort or liver dysfunction.

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References


FIG. 1  A Sigmoidoscopy indicates multiple chancres and indurated nodular mucosa located on the wall of the lower rectum. B Barium enema shows circumferential thickening of the lower rectal wall and multiple nodular mucosa.

FIG. 2  A Gastroscopic findings demonstrate multiple erosive lesions in whole gastric mucosa. (indigo carmine dye contrast) B A gastric biopsy specimen with antibody stain...
shows numerous brown staining spirochetes (arrow) in interstitium (*Treponema pallidum*
polyclonal antibody stain, ×400)