中文題目：病例報告：抗粒線體抗體陰性之原發性膽汁性肝硬化並存全身性紅斑性狼瘡之罕見案例

英文題目：A rare case report of anti-mitochondrial antibody-negative primary biliary cholangitis with coexistence of systemic lupus erythematosus

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[Introduction]

Primary biliary cholangitis (PBC) is a cholestatic disorder of unknown etiology. Antimitochondrial antibodies (AMA) was present in >90% patients diagnosed as PBC. Although autoimmune diseases often coexist, concomitant cases of systemic lupus erythematosus (SLE) and PBC are relatively uncommon. Patient diagnosed as PBC with negative AMA is even much rarer in concomitant cases of SLE and PBC.

[Case report]

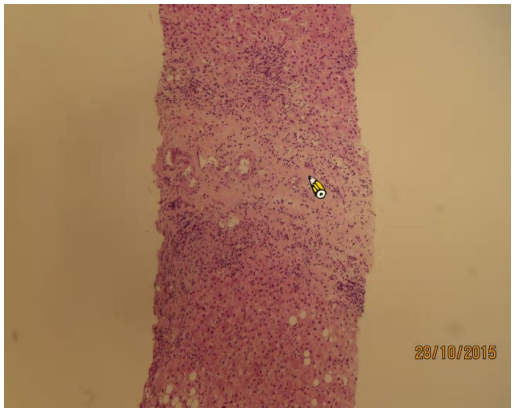
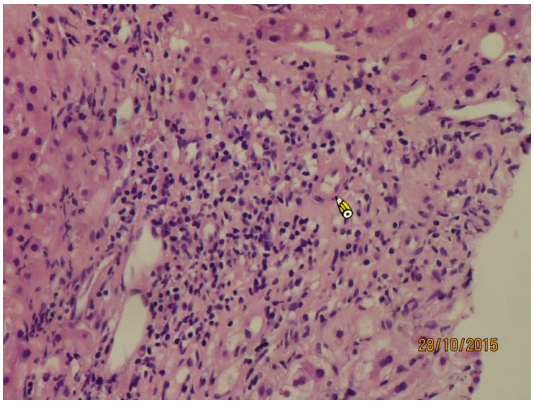
A 45-year-old woman has history of SLE on mycophenolate mofetil (MMF) 500 mg and prednisolone 10mg daily for recent years. She was referred to our rheumatology clinic due to abnormal liver enzymes (GGT, 1196 U/L; AST, 67 U/L; ALT, 161 U/L; ALP, 306 U/L; D-Bil, 0.4 mg/dL; T-Bil, 0.8 mg/dL; ALB, 4.0 g/dL) on 2012/03/19. For suspected type 1 autoimmune hepatitis (AIH), MMF was replaced by azathioprine 100mg daily, and prednisolone was titrated to 20 mg daily. The silymarin (75mg daily) was also administered empirically.

The liver enzymes were persistently abnormal, predominantly in cholestatic pattern, so she was referred to our hepatology clinic. She denied drug abuse or taking herb, and her father has uncertain liver disease. Pruritis for years was reported. Physical examinations showed dry eye and mouth, no jaundice, soft abdomen and no ascites. The blood test showed no evidence of Wilson's disease, infection of HBV, HCV, HIV, CMV or toxoplasma. The autoantibody test showed negative AMA, positive (1:20) ASMA, positive (1:1280, centromere) ANA, negative Anti-nDNA Ab, negative Anti-RNP, negative Anti-Sm, negative anti-Ribosomal-P antibody, positive SS-A/Ro antibody, negative SS-B/La antibody, negative antiphospholipid antibodies. The level of serum IgG, IgM, C3 and C4 were normal. Abdominal sonography revealed coarse liver parenchyma and splenomegaly. She underwent liver biopsy. The pathologic diagnosis was cirrhosis with bile duct damage and loss, and it is consistent with PBC.

She received high-dose ursodeoxycholic acid (UDCA) (15mg/kg) as standard therapy of PBC since 2012/08. However, serum level of ALP did not decline after 1 year of

UDCA treatment, and the signs of decompensated liver disease occurred (T-Bil, 1.4 mg/dL) since 2015.. On Jan-2015 , esophageal varices (F1) and portal hypertensive gastropathy were noted in the panendoscopy. The Fibroscan® on Jul-2015 also revealed significant cirrhosis(TE: 46.4kPa). She was referred to liver transplant evaluation in Dec-2016. Under the de-compensated cirrhosis (Jaundice, ascites and hypoalbunemina), she received cadaveric liver transplant in Jan-2019, and hyperbilirubinemia (T-Bil, 3.6 mg/dL), hypoalbuminemia (ALB, 3.0 g/dL), thrombocytopenia (76x10^3/μL) with severe splenomegaly (197.8 mm) at the time just before transplant. Following level of serum ALP and BIL improved and normalized in May-2019. However, the level of serum ALP elevated in recent months gradually, although it did not above two times the upper normal value. UDCA was administered back, and she is followed up in our transplant clinics regularly.

[Biopsy]

<table>
<tr><td colspan="2">Cirrhosis with bile duct damage and loss</td></tr>
<tr><td> 
</td><td> 
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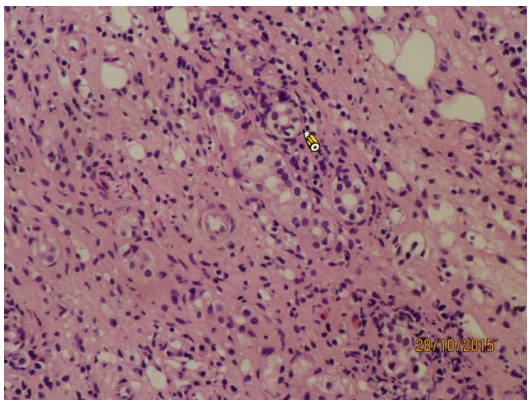
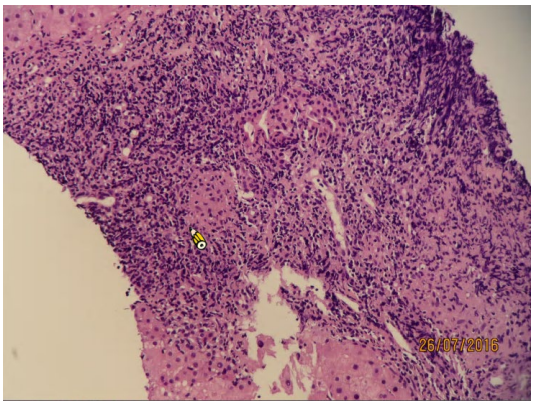
<tr><td>Some thicken fibrotic band with lymphocyte infiltration</td><td>No bile duct beside hepatic artery</td></tr>
<tr><td> 
</td><td> 
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<tr><td>Lymphocyte infiltrate to the epithelium of bile duct, called florid duct lesion</td><td>Granuloma formation is a another typical feature of PBC (another patient)</td></tr>
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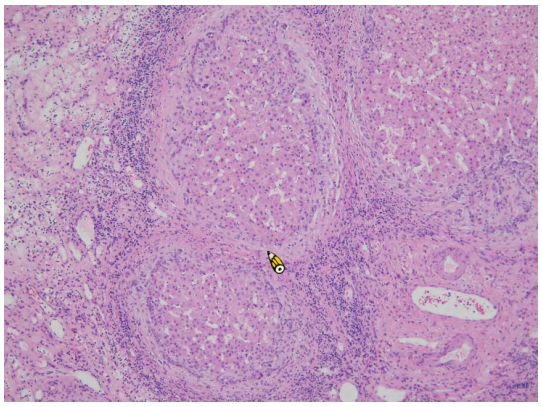	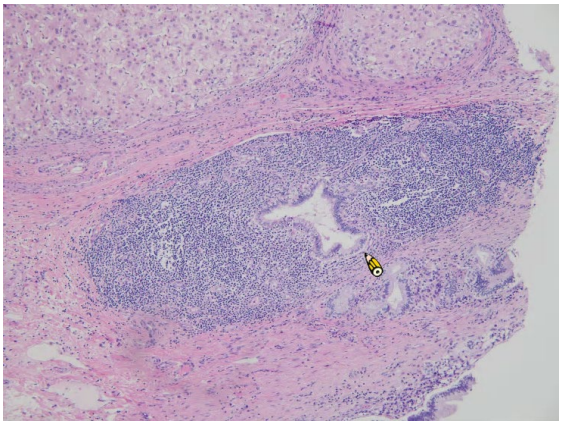
The white band is an edematous change of fibrotic band where is outside of infiltrated hepatocyte, called halo sign	Obvious florid duct lesion with ductocentric lymphocytic infiltration

[Discussion]

Primary biliary cholangitis (PBC) is a cholestatic disorder of unknown etiology with autoimmune features. In Asia–Pacific region, the incidence (8.55 cases per million per year) of PBC are higher than once expected (Na et al, 2019). It most often affects middle-aged woman with fatigue, jaundice and pruritits as most noticeable presentation. AMA was present in >90% patients diagnosed as PBC which could be diagnosed with positive AMA as well as unexplained elevated ALP two times above upper normal value for over 24 weeks. Liver biopsy is helpful but not necessary for definitive diagnosis, unless serology-negative PBC was suspected.

In a study enrolled 96 consecutive PBC patients between 1985 and 2006 at Taipei Veterans General Hospital, 85 were positive for AMA in serum, and 11 were negative. There were no significant differences in age, sex, clinical manifestations, liver biochemistries, histological findings between the AMA-negative and AMA-positive patients. Most observational studies supported that AMA levels could not be affected by treatments.

Although autoimmune diseases often coexist, concomitant cases of systemic lupus erythematosus (SLE) and PBC are uncommon. The incidence of coexisting PBC in patients with SLE is ≤2% (Toru, 2015). The well-known hepatoxicity of immunosuppressive medications for SLE may distort the clinical and laboratory findings of underlying autoimmune liver disease.

Patient diagnosed as PBC with negative AMA is even rarer in concomitant cases of

SLE and PBC. A few case reports noticed that the antibody titers of AMA repeatedly decrease and undergo negative conversion over time in approximately 1/3 of the SLE patients with concomitant AMA-positive PBC. Whether concomitant cases occur by chance or share a common immunological or genetic basis remains uncertain. The autoantibodites such as Anti-Nuclear-Antibody (ANA), anti-saccharomyces cerevisiae antibodies (ASCA), anti-neutrophil cytoplasmic Ab (ANCA) and anti-Sm Ab closely related to other autoimmune diseases were found in patients with PBC sometimes. These associations are extremely complicated and surely exert complex effects.

Regarding treatment, there was no significant difference in response to 1-year UDCA treatment between the AMA-negative and AMA-positive patients. About prognosis, the previous study showed no significant difference between these group, but recent study showed that there was a significantly reduced survival free of liver-related complications including transplantation and death in the AMA-negative patients (Juliusson et al, 2016). **Obeticholic acid (OCA), a bioavailable farnesoid X receptor (FXR) agonist. OCA reduces in the synthesis of biliary acids and reduces the reabsorption of biliary acids in the ileum. OCA is the second-line therapy for patients with PBC inadequate response to UDCA (Abenavoli et al, 2020). There was no study aim at FXR in AMA-negative PBC currently.**

In conclusion, we presented a SLE patient presented with transaminitis with poor response to immunosuppressive agents turned to be AMA-negative PBC after serial serology and liver biopsy proof. The treatment of AMA-negaitve PBC remains UDCA but the role of FXR in AMA-negative PBC may need further evaluation.