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# A Case of Autoimmune Cholangitis Associated with Sjögren's Syndrome and Arthropathy

Autoimmune cholangitis (AC) is a recently proposed entity that describes a specific group of patients presenting overlapping features of primary biliary cirrhosis (PBC) and autoimmune hepatitis. The disease is characterized by clinical cholestasis, high titer antinuclear antibody, negative antimitochondrial antibody, and histolologically, findings of PBC coexisting with varying degrees of parenchymal inflammation. In this report, we describe a patient with Sjögren's syndrome who fulfilled the diagnostic criteria of AC associated with unique arthropathy compatible with arthritis of PBC. This case illustrates the unusual coexistence of two diseases that may share similar pathogenic processes.

Key Words : *Autoimmune cholangitis, Sjögren's syndrome, Arthropathy*

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## INTRODUCTION

Autoimmune cholangitis (AC) has been recently described in patients who were initially thought to have primary biliary cirrhosis (PBC) with atypical presentation. These patients showed clinical and histologic findings compatible with PBC but differed from those in showing varying degrees of parenchymal inflammation and negative tests for serum antimitochondrial antibody (AMA). Instead, they show high titer antinuclear antibody (ANA) positivity. Herein we describe a patient with Sjögren's syndrome who had diagnostic characteristics compatible with AC and unique arthropathy.

## CASE REPORT

The patient, a 46-year-old woman visited our hospital due to hand joint pain in February, 1995. During the previous three years, she had experienced an insidious onset of intermittent arthralgia involving both hands, wrists, and shoulders. For the preceding two years, she had noted deformity of the distal interphalangeal (DIP) joints. Since her pain was tolerable, she did not seek medical care. She experienced triphasic acral cyanosis when exposed to cold or when she was under emotional stress. She reported a foreign body sensation in the eyes and an extremely dry mouth, limiting conversation without drinking water. Pruritis was associated.

Her medical history was unremarkable. In particular, she had no previous history of liver or biliary disease and no exposure to drugs, alcohol or chemicals. She also had no history of transfusion. There was no family history of liver disease.

Physical examination revealed a dry and red tongue with atrophy of filiform papillae. The salivary gland was not enlarged. The chest and heart were normal. The liver was not enlarged but the spleen was palpable 2 cm below the left costal margin. The DIP joints of the hands were tender with flexion deformity. The shoulders had bilateral tenderness without soft tissue swelling.

Initial laboratory investigations revealed severe anemia, with a hemoglobin level of 6.4 g/dl. The white blood cell count was $3.1 \times 10^9$/L and the platelet count was $106 \times 10^9$/L. The erythrocyte sedimentation rate (Westergren) was 65 mm/hour. Her liver function tests were abnormal with alkaline phosphatase (ALP) 837 IU/L (normal value, <115 IU/L), $\gamma$-glutamyl transpeptidase ($\gamma$GT) 412 IU/L (normal value, <25 IU/L), aspartate aminotransferase 49 IU/L (normal value, <20 IU/L), and

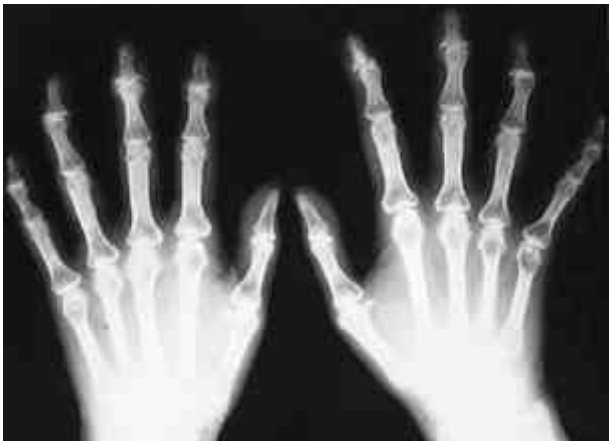

**Fig. 1.** Radiographic changes in the hands of the patient. Cortical erosions and joint space narrowings were seen on the distal interphalangeal joints.

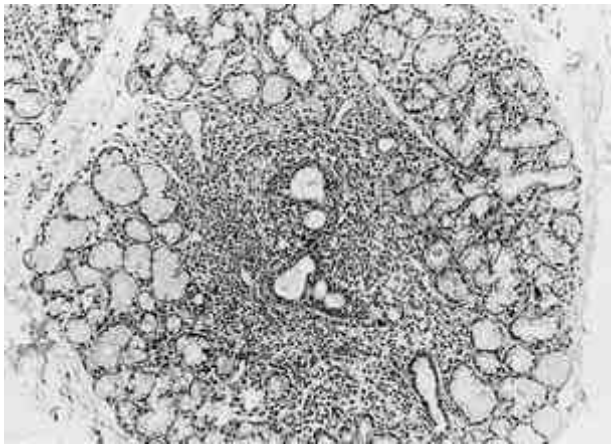

**Fig. 2.** Focal lymphocytic sialoadenitis of the labial salivary gland showing a focal aggregate of more than 50 lymphocytes (a focus) in normal appearing acini. (H&E, ×100).

alanine aminotransferase 49 IU/L (normal value, <20 IU/L). Total bilirubin was 1.3 mg/dl and direct bilirubin was 0.4 mg/dl. Urinalysis and renal function test results were normal. Antibodies to nuclear antigen was positive at a titer of 1:640 (centromere type) and anti-La was positive. AMA, SMA, anti-Ro, anti-DNA, anti-RNP, anti-Sm were all negative. Rheumatoid factor showed positive with a titer of 37.2 IU/ml (normal <20 IU/ml). $C_3$ was 65 mg/dl (normal 45-86 mg/dl) and $C_4$ 19 mg/dl (normal 11-47 mg/dl). Circulating immune complex (CIC) was 100 μg/ml (normal <25 μg/ml). Immunoglobulin G was 1,690 mg/dl (normal 1,014-1,949 mg/dl), immunoglobulin A 439 mg/dl (normal 117-426 mg/dl), and immunoglobulin M 329 mg/dl (50-271 mg/dl). Serologic testings for hepatitis B antigen and hepatitis C virus were negative. Antibody for hepatitis B surface antigen was positive. Hand X-ray showed joint space narrowing with marginal erosion on the DIP joints (Fig. 1). A computed tomography scan of the abdomen revealed diffuse heterogenous enhancement of the liver without focal lesion or biliary duct dilatation and marked splenomegaly. Salivary gland scintigraphy showed decreased activity of both submandibular glands and both parotid glands. Esophagogastroduodenoscopy revealed esophageal varices with recent evidence of bleeding. Schirmer test was positive. A biopsy of the labial salivary gland was performed and this showed focal lymphocytic sialadenitis with a focus score of 2 (focus defined as an agglomeration of at least 50 mononuclear cells; focus score defined as the number of foci/4 $mm^2$ of glandular tissue) (Fig. 2). Biopsied liver showed a relatively well preserved lobular architecture with widened portal tracts due to lymphocytic infiltration. Loss of bile ducts was revealed in most of the portal tracts, and one portal tract had a bile-duct lesion, which showed dense periductal inflammation and damage to the bile duct epithelium. The site of rupture of the bile duct showed an ill-defined granulomatous inflammation. There was moderate piecemeal necrosis with mild ductular proliferation. The lobular activity was mild with occasional acidophilic bodies and focal necrosis. These findings were compatible with a stage I to II PBC with unusual periportal activity (Fig. 3).

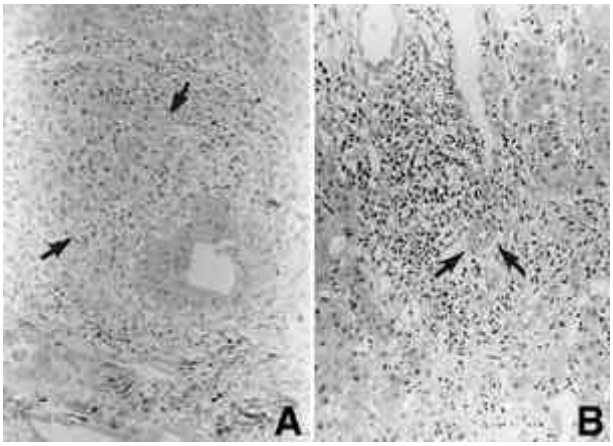


**Fig. 3.** Autoimmune cholangitis. (A) A bile duct lesion showing periductal inflammation and ill-defined granulomatous inflammation at the site of the bile duct rupture (arrows). (B) Small chronically inflamed portal tract with piecemeal necrosis showing a hepatic artery (arrows), but no bile duct. (H&E, × 100).

The patient was diagnosed as primary Sjögren's syndrome and AC, and prednisolone (60 mg/day) was begun. During the first 2 months of steroid treatment, ALP and γGT decreased to the level of 364 IU/L and 130 IU/L. The patient refused further steroid treatment due to the

appearance of cushingoid features. She went on health foods for several months and 2 months after stopping the steroids, her ALP level returned to the initial level. The hospital course was complicated by upper gastrointestinal bleeding due to ruptured esophageal varices and ascites. Azathioprine (100 mg/day) was started in March, 1996 due to persistently elevated ALP level. She is currently on azathioprine (50 mg/day) with an ALP level of 409 IU/L and she is conservatively managing ascites and esophageal varices with spironolactone and propranolol.

## DISCUSSION

Before Brunner et al. (1) described three patients with the clinical, biochemical and histological picture of PBC, without AMA but with ANA, and termed the condition as immunocholangitis, AC had been viewed as a spectrum of autoimmune hepatitis with cholestasis or as a subgroup of PBC with AMA negativity. There is still controversy whether or not to view this disease as a distinct entity. Clinically, AC is indistinguishable from PBC with various symptoms and signs related to cholestasis (2). But AC differs from PBC serologically by showing high titer ANA positivity instead of AMA. Among chronic liver conditions, the presence of ANA constitutes the diagnosis of autoimmune hepatitis (3). Chronic nonsuppurative destructive cholangitis remains the eminent domain of AMA. Although 7-14% of patients with PBC lack AMA, the more specific anti-M2 is found in virtually 100% of patients (4). Since PBC without AMA is difficult to consider and autoimmune hepatitis is not a disease of cholestasis, AC should be viewed as a distinct disease entity with characteristic clinical and serological features.

The pathogenic mechanism underlying AC is poorly understood. The predominant liver pathology of the AC is bile duct damage coexisting with varying degrees of parenchymal inflammation. AMA was implicated as playing an active role in the process of the bile duct injury of PBC. There is evidence suggesting that AMA in the form of autoantibodies against the pyruvate dehydrogenase-E2 may be the T cell epitope. This epitope may initiate the T-cell response leading to biliary epithelial damage (5). However, since AC shows bile duct damage in the absence of AMA, AMA cannot wholly explain the process of bile duct injury in these diseases.

The coexistence of Sjögren's syndrome with AC in our patient provided some foresight into the pathogenesis of AC. Sjögren's syndrome is an autoimmune disease characterized by lymphocytic infiltration of exocrine glands. Early lesions begin around ductal epithelial cells and as the disease proceeds, the infiltrate extends and replaces the functional tissue (6). The histopathologic features of Sjögren's syndrome patients strongly suggest that autoimmune insult is due to the attraction of lymphocytes by epithelial cells (7). In support of this view, epithelial cells have been shown to share common antigen, carbonic anhydrase II (8). AC shows similarity with Sjögren's syndrome in that dense lymphocytic infiltration surrounds the bile duct epithelium which extends to adjacent liver parenchyme. Bile duct epithelia also contain an abundance of carbonic anhydrase. There is evidence that an antibody to human carbonic anhydrase II is frequently detected in the sera of AC, which is uncommon in PBC (9). Since AC and Sjögren's syndrome share similar histopathologic findings and autoantibody profile, the association of these two diseases may represent a similar pathogenic process.

The natural history of AC appears to parallel the chronic, relentless progression of PBC. During the course of the disease, our patient showed various complications related to the progression of cirrhosis, despite the decrease in ALP level with steroid and azathioprine treatment. Some reports have shown a dramatic response to immunosuppressive drugs such as prednisone and azathioprine (1, 10), but others failed to demonstrate any significant effects of drug therapy (11). Generally, inflammatory components appear to improve but bile duct lesions seem irreversible. Since prednisone and azathioprine have been unsuccessful in the treatment of PBC, the unresponsiveness of AC was not unexpected as in our patient.

Our patient had a unique arthropathy involving the DIP joints the of hands. The DIP joints of the hands showed cortical bone erosions accompanied by joint space narrowing compatible with the arthritis of PBC. Ansell and Bywaters (12) first reported erosive bone lesions affecting large and small joints in three patients with PBC. In a Mayo clinic series, 9% of PBC patients exhibited an atypical polyarthritis which was termed the arthritis of PBC (13). Distinctive radiographic features have been reported in these patients with small, asymmetric, intracapsular, and non-articular cortical bone erosions, mainly involving the distal small joints of the hands accompanied by joint space narrowing (14). Our case demonstrates that arthropathy similar to PBC may also occur in AC.

On the basis of ANA positivity and similar histopathologic findings in AC and Sjögren's syndrome, we conclude that the coexistence of these two diseases in a patient may suggest diseases that share a similar pathogenic mechanism. The natural course of AC may be compatible with that of PBC. Clinicians should consider a diagnosis of AC in a clinical setting where PBC with AMA negativity is found.

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