



CASE REPORT

Diffuse Systemic Sclerosis in a Patient with Primary Biliary Cirrhosis and Autoimmune Hepatitis Overlap Syndrome: A Case Report

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Systemic sclerosis (SSc) is a chronic systemic disease of unknown etiology characterized by vasculopathy, excessive accumulation of extracellular matrix, and fibrosis of the skin and other internal organs. Although its etiology remains elusive, approximately one third of SSc patients presents with additional autoimmune disease, which suggests that an autoimmune mechanism is a major component of the underlying pathophysiology. On the other hand, primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) are two main autoimmune liver diseases. A 41-year-old female previously diagnosed with PBC/AIH overlap syndrome presented with multiple, painful brownish to erythematous firm patches on the hands, arms, axillae, neck, abdomen, and thighs. Laboratory work-up yielded positive results for anti-nuclear antibody, anti-Ro/Sjögren's-syndrome-related antigen A auto-antibodies, and perinuclear anti-neutrophil cytoplasmic antibodies while punch biopsy of her left hand showed characteristics that are consistent with scleroderma. Herein, we report the first case of a patient with diffuse cutaneous SSc and concurrent PBC/AIH overlap syndrome and suggest that this coexistence of multiple autoimmune diseases is not a coincidence but rather that a common autoimmune pathogenesis may exist. (*Ann Dermatol* 32(1) 69~73, 2020)

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-Keywords-

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INTRODUCTION

Systemic sclerosis (SSc) is a rare and chronic multisystem disease characterized by fibrosis of the skin and internal organs, especially the gastrointestinal tract. Although hepatobiliary involvement in SSc has been historically considered insignificant, recent investigations have revealed that autoimmune liver diseases (AILDs) are the most common form of liver diseases associated with SSc. Primary biliary cirrhosis (PBC), a chronic cholestatic liver disease, is an AILD that is most frequently observed in SSc patients. Autoimmune hepatitis (AIH) is another AILD that has been associated with SSc, which is characterized by interface hepatitis with lymphocyte and plasma cell infiltrates. Although uncommon, these two AILDs can coexist in one patient and the term PBC/AIH overlap syndrome (OS) is used to describe this phenomenon. Furthermore, a small number of PBC/AIH OS patients present with one or more additional extrahepatic autoimmune diseases. Regarding SSc, three cases of PBC/AIH OS with SSc have been previously reported in the literature. All three cases exhibited the limited cutaneous form of SSc (limited cutaneous systemic sclerosis [lcSSc])¹⁻³. Herein, we report the first case of a patient presenting with PBC/AIH OS with diffuse cutaneous SSc (diffuse cutaneous systemic sclerosis [dcSSc]) which suggests the presence of shared genetic and immunologic susceptibility factors in AILDs and SSc, irrespective of the cutaneous subtype of SSc.

CASE REPORT

A 41-year-old female presented with multiple, painful brownish to erythematous firm patches on the both hands, arms, axillae, thighs, neck, and abdomen for 2 years. Two months prior to her visit to our department, she had been referred to our hospital from a local clinic for abnormal liver function test results and was diagnosed as PBC/AIH OS by a hepatologist in the hospital. The initial laboratory work-up obtained from the department of internal medicine was as follows; hematological data showed normal white blood cell counts ($5,280/\text{mm}^3$), hemoglobin (12.7 g/dl), and platelet counts ($207,000/\text{mm}^3$); blood biochemi-

Table 1. Initial laboratory characteristics of the patient

Laboratory test	Result	Normal range
White blood count (mm^3)	5,280	3,000~9,000
Hemoglobin (g/dl)	12.7	11~15
Platelet count (mm^3)	207,000	140,000~400,000
Total bilirubin (mg/dl)	1.4	0.3~1.3
Direct bilirubin (mg/dl)	0.6	0.0~0.4
AST (IU/L)	113	0~34
ALT (IU/L)	62	0~40
ALP (IU/L)	618	30~120
GGT (IU/L)	529	4~34
Anti-HCV	Negative	-
Anti-HBc (IgG)	Negative	-
HbsAg	Negative	-
Anti-HBs	Positive	-
Immunoglobulin G (mg/dl)	3098	-
Immunoglobulin M (mg/dl)	594	-
Antinuclear antibodies	Positive (1:640), mixed speckled, anti-ribosome	-
p-ANCA	Positive	-
Anti-SSA	Positive	-
Anti-SSB	Negative	-
Anti-Scl-70 Ab	Negative	-
Anti-LKM-1 Ab	Negative	-
Anti-mitochondrial Ab	Negative	-

AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma glutamyltransferase, Anti-HCV: antibodies against hepatitis C virus, anti-HBc: antibody to hepatitis B core antigen, HbsAg: hepatitis B virus surface antigen, Anti-HBs: anti-hepatitis B surface antibody, p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies, Anti-SSA: anti-Sjögren's-syndrome-related antigen A, Anti-SSB: anti-Sjögren's-syndrome-related antigen B, Anti-Scl-70 Ab: anti-topoisomerase I antibody, Anti-LKM-1 Ab: anti-liver-kidney microsomal antibody, -: not available.

cal data revealed elevated total bilirubin (1.4 mg/dl), direct bilirubin (0.6 mg/dl), aspartate aminotransferase (113 IU/L), alanine aminotransferase (62 IU/L), alkaline phosphatase (618 IU/L), γ -guanosine triphosphate (529 IU/L), IgG (3,098 mg/dl), and IgM (594 mg/dl). Anti-nuclear antibody (ANA titer 1:640; mixed speckled), perinuclear anti-neutrophil cytoplasmic antibodies, and anti-Ro/Sjögren's-syndrome-related antigen A autoantibodies were positive (Table 1). Liver biopsy showed moderate portal inflammation with lymphoplasma cells, moderate lobular activity, mild fibrosis, and bile duct with lymphocytic cholangitis (Fig. 1). She fulfilled the diagnostic criteria for PBC as well as AIH proposed by the American Association for the Study of Liver Disease and was diagnosed as PBC/AIH OS^{4,5}. She was then referred to our department for a thorough investigation of her skin lesions.

The skin lesions initially developed 2 years ago starting from her fingers, which progressively spread to the hands, forearms, axillae, and trunk. Diffusely puffy hands with shiny skin suggesting impending skin thickening were observed (Fig. 2A). An indurated subcutaneous nodule was found on her left thumb (Fig. 2B). Widespread discolored indurated patches surrounded by hyperpigmented areas were observed on the abdomen and back (Fig. 2C, D). Diffuse hard patches with salt-and-pepper hypopigmentation were seen on both axillae (Fig. 2E, F). She complained of pain and tightness of the skin lesions. Physical examination revealed sclerodactyly and Raynaud's phenomenon. With the impression of scleroderma, a punch biopsy of her left hand was performed. The skin biopsy revealed a "square" appearance with thickened, closely packed collagen bundles in the reticular dermis (Fig. 3). These histological findings were consistent with scleroderma. By fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism criteria for SSc, a fi-

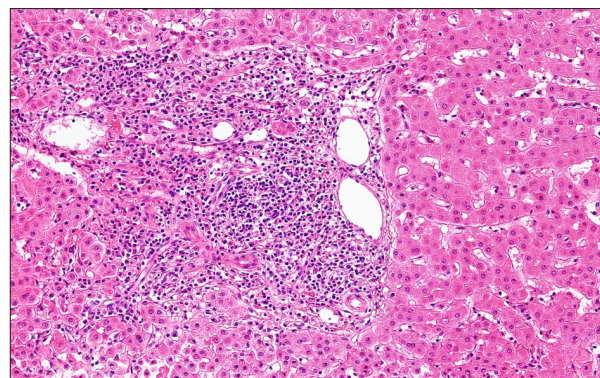


Fig. 1. Liver specimen showed a moderate portal inflammation with abundant lymphoplasma cells and mild bile duct damage with lymphocytic cholangitis (hematoxylin and eosin, $\times 200$).

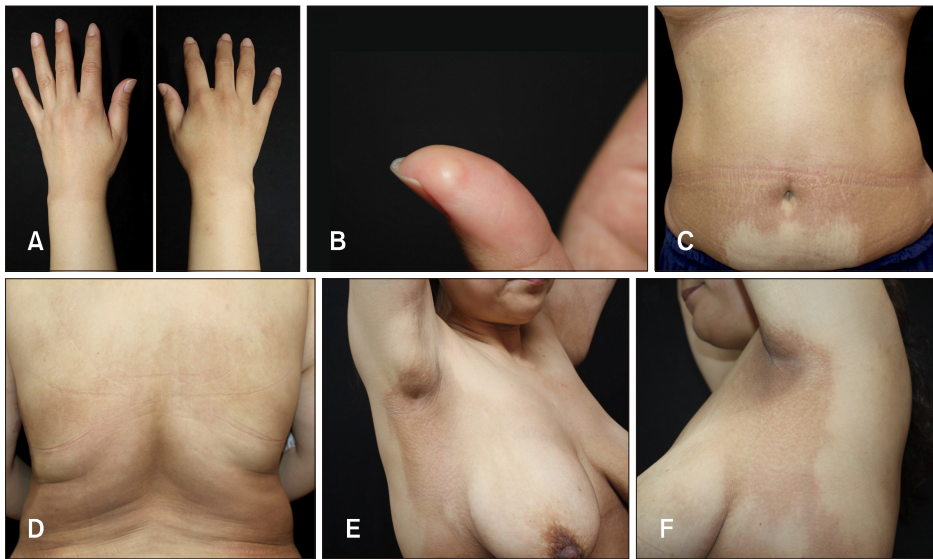


Fig. 2. Clinical photographs of the patient on initial visit. (A) Hands, diffusely puffy hands with shiny skin. (B) Left thumb, indurated subcutaneous nodule. (C) Abdomen, widespread discolored indurated patches surrounded by hyperpigmented areas. (D) Back, linear band of firm plaques and pigmentary changes. (E, F) Axillae, salt-and-pepper hypopigmentation and diffuse hyperpigmentation.

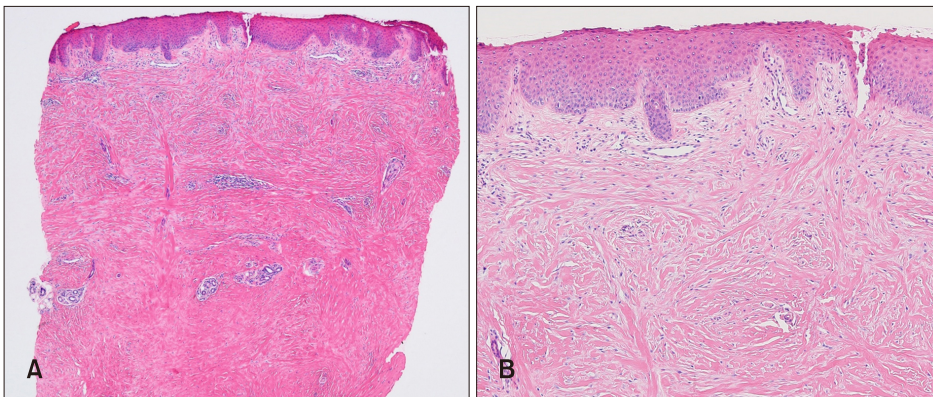


Fig. 3. Finger specimen. (A) A 'square appearance' in a punch biopsy (hematoxylin and eosin [H&E], $\times 40$). (B) Collagenous fibrosis in the upper and reticular dermis (H&E, $\times 100$).

nal diagnosis of SSc was made⁶. We received the patient's consent form about publishing all photographic materials.

DISCUSSION

Historically, hepatobiliary involvement in SSc has not been considered characteristic; however, recent investigations have revealed a higher prevalence of liver disturbances in SSc patients ranging from 37% to 52%⁷. Interestingly, primary AILDs accounted for 77% of all liver diseases in SSc patients with PBC as the main cause (57%) followed by AIH (16%)⁷. Previously, some researchers argued that hepatobiliary involvement in SSc occurs through chance and is possibly related to coexisting liver steatosis, viral infections, or drug-induced toxicity from SSc treatment⁸. However, we suggest that there may exist a shared autoimmune basis in AILDs and SSc etiology. Our patient supports this argument since she presented with SSc and an OS of two AILDs. Her laboratory findings were positive

for multiple autoantibodies and PBC/AIH OS was diagnosed before the discovery of SSc or any therapeutic interventions regarding SSc. There was no evidence for other causes of liver dysfunction, such as alcohol abuse, drugs, or viral infection, which could idiosyncratically cause hepatitis, including those that can mimic PBC or AIH.

PBC, AIH, and SSc are disorders involving a complex interaction between genetic and environmental factors; environmental trigger in a background of genetic defects in immune regulation induces persistent inflammation and breakdown of self-tolerance. Regarding the genetics underlying SSc and AILDs, many common genetic loci of PBC and SSc have been identified, including several human leukocyte antigen (HLA) regions (HLA-DRB1, DQA1, and DQB1) and non-HLA regions (interferon regulatory factor 5 and signal transducer and activator of transcription 4)^{9,10}. With this genetic background, several triggering events, such as viruses, herbs, or the use of antibiotics in AIH, urinary tract infections, vaginal infections, and ciga-

rette smoking in PBC, and viral or bacterial infections and environmental toxins in SSc, initiate autoimmune attack¹¹⁻¹³. Apart from the genetic and environmental factors, the adaptive immunity also seems to play a pivotal role since the dysregulation of Th17 and Tregs have been commonly noted in SSc, PBC and AIH¹⁴⁻¹⁶. Interleukin-6, an important mediator in SSc which is also elevated in the hepatocytes of AILDs, may polarize lymphocytes, favoring Th17 differentiation or macrophages^{17,18}.

To our knowledge, this is the first report of an association between dcSSc and PBC/AIH OS. In the literature, all three previous cases of PBC/AIH OS and SSc were in the limited cutaneous form¹⁻³. Based on these findings, some authors have suggested that the lcSSc subset may have a distinct pathogenesis with a greater autoimmune background⁷. However, our patient's condition shows that dcSSc can also coexist with PBC/AIH OS and that a common autoimmune basis may exist between AILDs and SSc—irrespective of the SSc cutaneous subtype. In conclusion, we suggest that a common autoimmune mechanism may underlie AILDs and SSc in etiology and that patients with PBC/AIH OS should be closely monitored for the risk of developing SSc and vice versa. Finally, this common autoimmune basis should be further investigated for better understanding of the disease and development of novel therapeutic options.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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