# A case of primary biliary cirrhosis, CREST and Sjögren's syndrome overlap presented with severe esophageal variceal bleeding

Mehmet Sahin*, Ulku Sarıtas**, Nurhayat Ozkan***, Sevket Ercan Tunc*, Nermin Karahan****

*Department of Internal Medicine, Division of Rheumatology, Suleyman Demirel University, Faculty of Medicine, Isparta, Turkey
**Department of Internal Medicine, Division of Gastroenterology, Suleyman Demirel University, Faculty of Medicine, Isparta, Turkey
***Department of Internal Medicine, Suleyman Demirel University, Faculty of Medicine, Isparta, Turkey
****Department of Pathology, Suleyman Demirel University, Faculty of Medicine, Isparta, Turkey

## Özet

**Ciddi Özafagus Varis Kanaması İle Başvuran, CREST Ve Sjögren Sendromu İle Çakışma Yapan Bir Primer Biliyer Siroz Vakası**

Primer biliyer sirozda karaciğer hasarının mekanizması otoimmüniteye ait deliller olmasına ve çeşitli otoimmün hastalıklarla çakışma yapabilmesine rağmen tam olarak bilinmemektedir. Burada masif hematemez yakınması ile başvuran 52 yaşındaki bir kadın hastayı takdim ediyoruz. Hastaya yapılan üst gastrointestinal sistem endoskopisinde rüptüre özafageal varisler tespit edildi. İki kez başarılı bir şekilde hastaya skleroterapi yapıldı. Sonrasında hastada belirgin asit ortaya çıktı. Buna rağmen hasta tedaviden sonraki 3.günde kendisini daha iyi hissediyordu. Hastaya klinik bulgular, yüksek düzeydeki alkalen fosfataz ve immünglobülin M düzeyleri, antimitokondrial antikor ve antisentromer antikor pozitifliği ve minor tükrük bezi biyopsisindeki pozitif sonuçlar ışığı altında sınırlı tipte sistemik skleroz ve Sjögren sendromu ile çakışma yapan primer biliyer siroz tanısı konuldu. Diğer bir bulgu ise mitral stenoz idi. Hastaya klinik bulguların semptomatik tedavisi için propranolol ve primer biliyer siroz tedavisine yönelik ursodeoksikolik asit verildi.

**Anahtar kelimeler:** özafageal varis kanaması, sınırlı tipte sistemik sklerozis, primer biliyer siroz, Raynaud fenomeni, Sjögren sendromu.

## Abstract

Despite the evidences indicate that it can be autoimmune in origin the exact mechanism of liver damage in primary biliary cirrhosis is unknown, and may overlap with a variety of autoimmune-mediated diseases. Here, we report a 52-year-old female patient presented with massive hematemesis. Upper gastrointestinal endoscopy showed ruptured esophageal varices. Sclerotherapy was applied two times successfully. The patient developed manifest ascite afterwards. However, she felt better three days after the treatment. She was diagnosed as overlapping of limited cutaneous systemic sclerosis, Sjögren's syndrome and primary biliary cirrhosis based on clinical features, high levels of alkalen phosphatase, positive anti-mitochondrial and anticentromer antibodies, high titers of serum immunoglobulin M and positive minor salivary gland biopsy findings. Another finding was mitral stenosis. The patient was adequately managed symptomatically by propranolol treatment for clinical findings and also ursodeoxycholic acid for primary biliary cirrhosis.

**Key words:** esophageal variceal bleeding, limited systemic sclerosis, primary biliary cirrhosis, Raynaud's phenomenon, Sjögren's syndrome

**Yazışma Adresi:** Mehmet Sahin, MD
SDÜ Tıp Fakultesi, İç Hastalıkları AD, 32260, Isparta, Turkey.
**Phone:** 00 90 246 2112613 Fax: 00 90 246 2371758
**E-mail:** mehmetsahin66@hotmail.com

## Introduction

Primary biliary cirrhosis (PBC) is a chronic progressive and cholestatic liver disease that seems to be autoimmune in origin. It is characterized by a destruction of the bile ducts, both the septal and smaller intralobular ducts; portal inflammation with scarring; and extension of the inflammatory process into the liver parenchyma, causing hepatocyte destruction and extensive fibrosis. Ultimately, liver cirrhosis and liver failure ensue (1).

Systemic sclerosis (SSc) is a connective tissue disease characterized by inflammatory, fibrotic and degenerative changes. Patients with limited cutaneous systemic sclerosis (lcSSc) have skin involvement limited to the hands, face, feet and forearm and it is known as CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias) syndrome (2,3). Sjögren's syndrome (SS) is also an autoimmune disease that exists in two clinical forms: primary and secondary. Secondary SS is clinically diagnosed when dry eyes and dry mouth coexist with a systemic autoimmune disease (4). Patients with PBC may often have another immune-related disease such as Sjögren's syndrome, rheumatoid arthritis, Hashimoto's thyroiditis or scleroderma (5-7).

We report here a patient with PBC coexisting with CREST and Sjögren's syndrome who presented initially with severe esophageal variceal bleeding. The patient had also mitral stenosis.

## Case Report

A 52 year-old woman presented with sypmtoms of severe nausea, weight loss, generalized abdominal pain and massive hematemesis. A medical history revealed that the patient was diagnosed as having Raynaud's phenomenon and arthralgia ten years before possibly due to undifferentiated collagen vascular disease, without regular follow up and treatment. About one week before admission, she was told that she had pain and swelling on parotid gland and was prescriped naproxen sodium. Two days before admission, a burning epigastric pain without radiation was developed but she had continued to take her medications. She suffered from a dryness associated with a sensation of sand in her eye and dry mouth. The patient had no complaints of pruritis or jaundice. On physical examination, the patient appeared to be fatigued and acutely ill. The blood pressure was 90/60 mmHg and the pulse rate was 105/min. The conjunctiva was pale. The patient had a mask like face, pinched nose and microstomia. She had telangiectasias on face and had radial furrowing around her mouth. The oral mucosa and tongue appeared dry. Sclerodactly and pitting ulcers over her fingertips were present. The skin especially thickened and adhered to subcutane tissue on face, hands and distal extremities with no skin involvement on the trunk and proximal extremities. The lungs were normal on physical examination and chest radiography. Cardiovascular examination revealed middiastolic murmur at apex. Abdominal examination revealed hyperactive bowel sounds on auscultation. The edge of the liver descended 2.5 cm below the right costal margin. The spleen was palpable on margin of left arcus costarum. Rectal examination revealed melena. On admission, hemoglobin was (Hb) 8.5 g/dl, hematocrit %25.3, white blood cells (WBC) 11 900/$mm^3$, platelet 152 000/$mm^3$, erythrocyte sedimentation rate (ESR) 60mm/h, prothrombin time 13.6 second, blood urea nitrogen 46 mg/dl (normal 7-25.7), creatinin 1.2 mg/dl, AST 36 IU/L, ALT 58 IU/L, GGT 41 IU/L, ALP 237 IU/L, total serum bilirubin 1.57 mg/dl, direct bilirubin 0.7 mg/dl, albumin 3.1 mg/dl. Upper gastrointestinal endoscopy revealed ruptured esophageal varices and active bleeding. Sclerotherapy was applied two times because of the persisting bleeding. During this period, the patient was given proton pump inhibitors, antiacids, lactulose, intravenous fluid and several blood transfusions. Hb level was increased to 9.5 g/dl and stabilized. However, ascite was manifested and she began to have intermittent episodes of fever (about 38 ºC). Ascite was transudate in character. All culture specimens were sterile and intravenous administration of ceftriaxon 2g/d and diuretic treatment in combination of spironolactone with furosemid were begun. On the third day, the patient felt considerably better and the body temperature was normal. Afterwards the etiology of hepatic failure was investigated. Since, the presence of arthralgia, Raynaud's phenomenon, eye and mouth dryness, telangiectasia and findings of skin, she was considered to have an overlap syndrome. Schirmer's test was performed, and a significant decrease in tear production was found in both eyes (right and left eyes were found as 2 and 3 mm). Serological tests of hepatitis B and C viruses were all negative. Thyroid function tests were normal and thyroid autoantibodies were negative. The concentrations of IgG, IgA, and IgM were 761 mg/dl (normal 700-1600), 102 mg/dl (normal 70-400), and 265 mg/dl (normal 40-230),

respectively. Antinuclear antibody (ANA; in speckled pattern), anticentromere antibody and antimitochondrial antibody (AMA) were positive. Anti-scl-70, anti-SS-A, anti-SS-B and ANCA were negative. Rheumatoid factor, C3, C4, ferritin, urinalysis, chest radiography and ECG were all normal. An abdominal ultrasonographic examination revealed hepatosplenomegaly, heterogenity in hepatic parenchyma, large amounts of ascites and portal vein dilatation that measured 14.5 mm in diameter on portal space and no dilatation in bile ducts. Transthorasic echocardiography revealed pulmonary hypertension (30 mmHg). Mitral valve area was 1.8 $cm^2$. There was a mild tricuspid regurgitation. Left atrium was 39 mm (normal <40). The diagnosis of SS was made by minor salivary gland biopsy which revealed a dense parenchymal lymphocytic infiltration consistent with SS (Chisholm grade 3) (Fig 1).

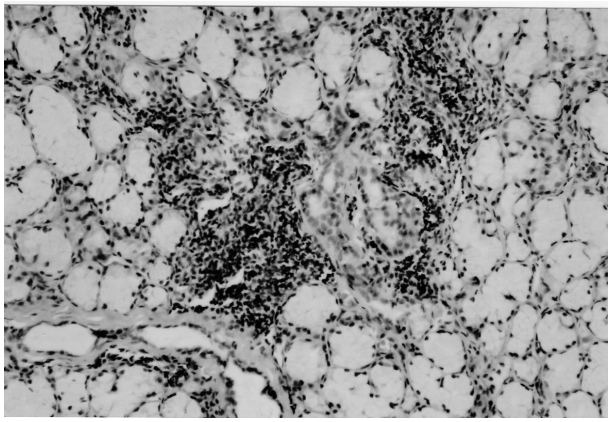

Fig 1: Minor salivary gland biopsy shows a dense lymphocytic infiltration consistent with Sjögren's syndrome (H&E x 200).

Based on the clinical examination and laboratory investigations, a diagnosis of PBC associated with CREST syndrome and SS was made. Propranolol 100 mg/d (by giving attention for Raynaud's phenomenon) and ursodeoxycholic acid at 750mg/d were begun for portal hypertension and PBC, respectively. Also an artificial tear drop was prescribed to increase salivary flow. Clinical findings were significantly improved. Bleeding was stopped and ascite was regressed. Three weeks later, the patient was discharged with the advices to follow up in the outpatient clinic.

## Discussion

In the presented case, she had a long history of possibly overlapping autoimmune disorders, including CREST syndrome, SS and PBC. PBC may overlap with other autoimmune disorders (5, 6, 13, 14). Firstly, Murray-Lyon et al. (10) reported two patients with PBC complicated with scleroderma, one case of which had CREST syndrome, and suggested that the association of the two diseases may be due to a common autoimmune mechanism. Afterwards, Reynolds et al. [11] reported six patients with PBC and CREST syndrome. In a study from the Mayo Clinic evaluating 113 patients with PBC, 84% of the patients had at least one other autoimmune disorder; 18% of these patients had SSc (6). Secondary SS may be associated with a systemic autoimmune disease such as SSc or occasionally PBC. Dry mouth and dry eyes, which are the classical symptoms of SS, have been reported to occur about one third of patients with PBC and about 40% of PBC patients have autoantibodies characteristically found in SS (13,14). The prognosis of patients with PBC and CREST overlapping is better than that of patients with PBC alone. Despite, Tojo et al (17) reported the survival rate of patients with PBC and CREST syndrome 10 years after the disease onset (87.5%) is better than that of patients with PBC alone (45.5%), the patients overlapping with CREST had a greater number of esophageal varices. Similarly, a better prognosis for survival was found in PBC patients who have ANA positivity (18). Most PBC patients may have no subjective symptoms. Such a relatively benign state may last for many years, with a median duration of 10 to 15 years. Routine laboratory studies can raise suspicions regarding the presence of the disease. Eosophageal variceal bleeding and progressive ascite may be presenting symptoms in a patient with PBC and usually occur late in the course of PBC. The findings of our patient were similiar with the reported series (16-18). Despite she was asymptomatic for years, portal hypertension and hematemesis from esophageal varices on admission were the signals of liver cirrhosis in our patient. These initial symptoms and rheumatologic findings led us to consider autoimmune liver diseases including primary biliary cirrhosis (PBC) to explain the liver problems in our patient.

In the presented case PBC is accompanied by CREST syndrome and SS. Limited skin involvement, long history of Raynaud's phenomenon, pulmonary arterial hypertension, positive ANA and anticentromer antibodies were suggested the diagnosis of CREST syndrome. SS was diagnosed on the basis of xerostomia and xerophtalmia, and a positive minor salivary gland biopsy. Although the autoantibodies

to SS-A and SS-B serve as diagnostic markers for SS, the incidence of these antibodies has been reported to be lower in patients with SS especially secondary to PBC. Hansen et al (15) found autoantibodies to SS-B in 38% of their PBC patients and 67% of their primary SS patients. SS-A autoantibody was not detected in their PBC patients. In our patient, the antibodies to SS-A and SS-B were both negative. Our patient also had mitral stenosis in addition to pulmonary hypertension. Myocardial lesions (fibrosis), conduction abnormalities and pericarditis occur frequently in patients with progressive systemic sclerosis. Involvement of cardiac valves in systemic sclerosis has been reported sporadically. Oram et al (19) reported valvular lesions in five out of twenty eight cases of scleroderma culled from the literature. In an autopsy study of 58 patients with systemic sclerosis D'Angelo et al (20) reported that the prevalence of mitral valvular abnormalities is 38%. Our patient had clinically middiastolic murmur at apex, which was considered mitral stenosis and confirmed by echocardiography. Since, she had no previous history of acute rheumatic fever, we thought that valve involvement could be due to systemic sclerosis. Pulmonary arterial hypertension revealed by echocardiography could be due to mitral stenosis or CREST syndrome, which is also present in our patient.

Unfortunately, in such patients, the treatment is symptomatic. Thus, the patient was given symptomatic treatment for Raynaud's phenomenon, dry mouth and dry eyes. We began ursodeoxycholic acid treatment for PBC. The only recognized effective treatment to improve the outcome of a progressive PBC is liver transplantation (12).

In conclusion, although the exact mechanism of the liver damage is unknown in PBC, the evidences indicate that it can be of autoimmune in origin and may associate with other immune related disorders. It should be kept in mind that PBC can be associated with CREST syndrome and SS, and the patients with PBC may be asymptomatic for years.

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