Henry Ford Hospital Medical Journal

Volume 21 | Number 3 Article 4

9-1973

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Henry Ford Hosp. Med. Journal
Vol. 21, No. 3, 1973

Primary Biliary Cirrhosis with Systemic Sclerosis

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Two patients with combined biliary cirrhosis and scleroderma are described. Both patients also presented features of the CRST syndrome, namely Raynaud's phenomenon, and telangiectasiae. Nine previously reported cases are reviewed and the clinical data suggest that a common underlying immunologic basis may account for both clinical conditions.

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PRIMARY biliary cirrhosis is an unusual chronic liver disease found in middle-aged women, characterized by clinical and laboratory alterations of liver dysfunction due to impairment of bile excretion and progressive cell destruction around the intra-hepatic bile ducts.

To our knowledge there have been only nine well documented cases of combined primary biliary cirrhosis and scleroderma.[1-4] Most of these cases have also had some of the features of the CRST syndrome originally described by Winterbauer in 1964.[5] The CRST syndrome is characterized by the presence of calcinosis of the skin, Raynaud's phenomenon, sclerodactyly and telangiectasiae. In this paper we describe two patients with the diagnosis of both primary biliary cirrhosis and systemic sclerosis, each patient showing distinct expressions of the immunological and pathological alterations of these diseases.

Case Report I

A 48-year-old white woman was admitted to the Henry Ford Hospital on January 31, 1972, for evaluation of pruritus, jaundice and occasional post-prandial vomiting over a six-month period. Ten years earlier, a diagnosis of chronic cholecystitis had been made. Episodes of Raynaud's phenomenon and mild dysphagia had been observed since 1965. In May, 1967, she had been hospitalized because of suspected herniation of a cervical disc with mild nerve root compression. Conservative

management was prescribed. Laboratory studies at that time showed that the alkaline phosphatase was 39 Bodansky units; SGOT, 80 units; ANF, strongly speckled; DRAT, 1:320; BSP, 5%; prothrombin time, 14 seconds. Upper gastrointestinal series revealed a small hiatal hernia with esophageal motility alterations consistent with scleroderma. Microscopic examination of a percutaneous liver biopsy (Figure 1) showed moderate increase of fibrous tissue in all the portal triads. In one of these there was seen a granuloma formation with epithelioid cells and some eosinophils. Serological studies for infectious granulomatous disease were repeatedly negative.

In December, 1967, the patient was readmitted because of nasal and peri-rectal abscesses which were treated with drainage and antibiotic therapy. Repeat percutaneous liver needle biopsy and microscopic study showed a few areas of lymphocytic infiltration in the portal regions.

In January, 1968, an esophagomanometric study was reported as characteristic of involvement of the esophagus by systemic sclerosis. At this time she underwent a cholecystectomy and repair of the hiatal hernia. Operative cholangiogram did not reveal any defects in the hepatic biliary tract. A liver biopsy showed infiltrates of lymphocytes and plasma cells around the portal triads. Enlarged lymph nodes at the common duct and superior aspect of the pancreas were diagnosed as reactive follicular hyperplasia. The gallbladder had changes of chronic cholecystitis with cholelithiasis. After surgery the patient developed a stricture of the distal esophagus which accentuated her dysphagia, but esophageal dilations were performed with excellent results.

In 1968, physical examination showed a well-developed and well-nourished woman with mild jaundice and having several areas of skin excoriations secondary to scratching. The skin was somewhat tight and thickened over the fingers and face. There were several telangiectasiae on her face and mucosa of the lower lip and neck. The heart and lungs were normal. The liver and spleen were moderately enlarged. There was no evidence of sclerodactyly, calcinosis or xanthomas.

Laboratory studies revealed a hemoglobin of 15.6 gm%; hematocrit, 46.9%; white blood cell with differential count of 63% neutrophils; 3% bands; 8% eosinophils; 8% lymphocytes; 5% monocytes. Sedimentation rate was 36 mm/hour, and VDRL non-reactive. Blood urea nitrogen, creatinine, calcium, phosphorous and electrolytes were within normal limits. Prothrombin time was 12 seconds. Plasma fibrinogen was 480 mg%. Bilirubin, total 2.95 mg%, direct 1.07 mg%; SGOT, 120 units; LDH, 415 units; total cholesterol, 450 mg%; serum triglycerides, 215 mg%; total lipids, 1540 mg%. Serum lipoprotein electrophoresis, alpha lipoprotein 246; pre-beta lipoprotein 308; beta lipoprotein 986; total lipids 1540. Serum protein electrophoresis - total protein 8 gm%; albumin 3.71 gm%; alpha-I globulin 0.53; alpha II globulin 0.85; beta globulin 1.38; gamma globulin 1.54. Immunoglobulin electrophoresis, IgA 173 mg% (normal 30-135 mg%); IgG 888 mg% (normal 600-1400 mg%); IgM 658 mg% (normal 30-120 mg %); IgE less than 0.04 mg%. Australian antigen was absent as was fetoglobulin. Numerous LE preparations were negative. Anti-nuclear factor study revealed strong speckles and weak homogeneous fluorescence strongly suggestive of scleroderma.[6] Cryoglobulins were negative and the DRAT-absorbed titer was 1:2560. Smooth muscle antibodies were negative, but mitochondrial antibodies were positive at 1:80 serum dilution.

The chest x-ray was negative. The esophagus by cine roentgenography was found to be atonic, peristaltic waves were absent and the esophagus did not empty in a recumbent position. There was a small hiatal hernia. Esophageal manometry again revealed almost complete absence of peristaltic activity throughout the body of the esophagus. The stomach, small bowel and colon x-rays were normal.

Liver scan showed hepatomegaly without intrinsic defects. A percutaneous liver biopsy done at this time revealed changes limited to the portal areas where an increased number of bile canaliculi and round cell infiltration were seen. Each portal region was expanded by fibrosis which fanned out as thin bands making early lobular changes although no evidence of regenerating nodule formation was recognized. Peri-portal piecemeal necrosis of hepatic cells and some degree of degenerative changes of canaliculi were noted as well. There was no evidence of bile stasis. There was a non-specific Kupffer cell proliferation in focal areas. All these changes were consistent with the diagnosis of primary biliary cirrhosis.

Tuberculin skin tests were negative. The dermatologic consultant considered the skin changes non-specific and probably due to asteatosis and scratching. Skin biopsies taken from sites on the abdomen (during the

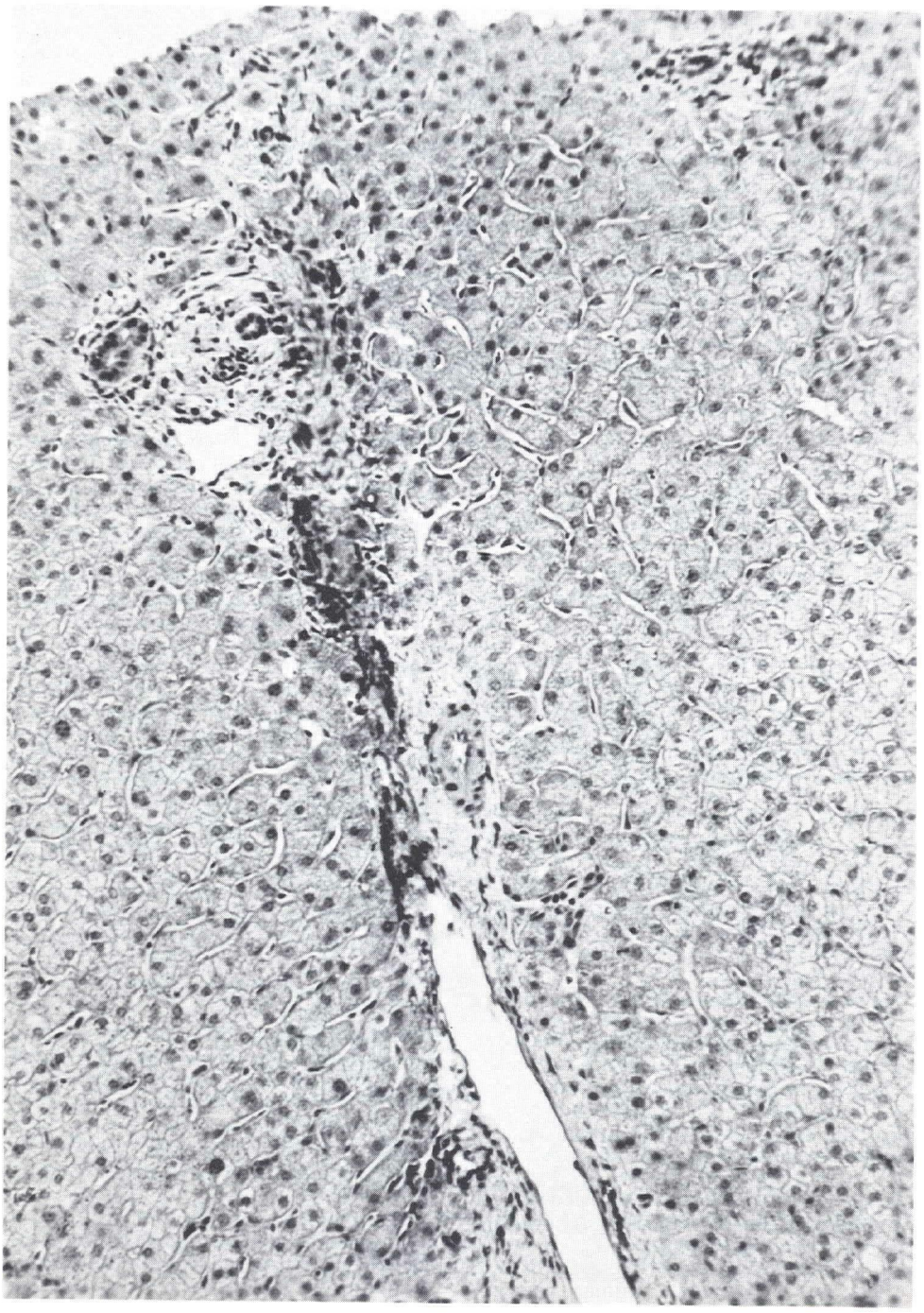

Figure 1
Needle biopsy of the liver from Case I showing periportal fibrous reaction. (184x)

cholecystectomy procedure) and the upper arm did not show the pathologic changes of scleroderma or calcinosis.

Case Report II

This 48-year-old home economics teacher was well until 1967 when she noticed that her skin was getting darker. Four years later she had an episode of transitory left hemiparesis which her physician attributed to cerebrovascular insufficiency. In February, 1972, she noted pruritus and when hepatosplenomegaly was found on physical examination, she was referred to Henry Ford Hospital. At that time she mentioned pain and bluish discoloration of the finger tips upon exposure to cold.

Laboratory data revealed the following abnormalities:

Bilirubin, 4.4 mg%; SGOT, 130 units; alkaline phosphatase, 35 Bodansky units; cholesterol, 360 mg%; triglycerides, 373 mg %; alpha and beta lipoproteins, 266 and 798 mg %; total lipids, 1260 mg %; serum albumin, 3.56 gm%; alpha-I, alpha-II and beta globulins, 0.44, 0.94 and 1.23 gm% respectively; serum iron, 207 mcg%; BSP, 33% retention; two-hour post-prandial sugar, 180 mg%. Immunoglobulin electrophoresis revealed an IgM of 151 mg%. Serum ceruloplasmin was 169 mcg%. Anti-nuclear factor was strongly positive, showing a pattern consistent with a diagnosis of scleroderma.

Urinalysis and complete blood count was normal. The blood urea nitrogen, creatinine and electrolytes were all normal. The peripheral blood smear and LE preparation were negative. VDRL was non-reactive. Stools were positive for bile. Skin tests for tuberculosis and histoplasmosis were negative.

The electrocardiogram showed an incomplete right bundle branch block with Q waves in Leads II, III and aVf. Chest x-ray, skull x-ray, intravenous pyelogram, double dose oral cholecystogram, liver scan, brain scan, and electroencephalogram were all normal. Metastatic survey showed mild demineralization without evidence of destructive lesions.

A percutaneous liver biopsy revealed minimal periportal fibrosis and cholestasis with moderate round cell infiltration.

Diagnoses were made of primary biliary cirrhosis with hyperlipidemia and systemic sclerosis with Raynaud's syndrome. The patient was sent home to await the result of an antimitochondrial antibody test which proved to be negative. A repeat study eight months later was also negative. In the meantime, her status remained stable and she was free of pruritus as long as she took cholestyramine. Because the antimitochondrial antibody tests were negative, she was re-admitted to Henry Ford Hospital November 5, 1972, for a duodenoscopic retrograde cholangiogram to exclude extrahepatic biliary obstruction.

Physical examination this time revealed a jaundiced woman in no discomfort. The skin was thickened and pigmented, particularly on the hands. The remainder of the examination was unremarkable except for a spleen tip palpable 3 cm below the left costal margin.

The laboratory data included the following:

Hemoglobin was 13.7 gm%; hematocrit was 41.9%; white blood cell count was 5,000 with 76% segmented neutrophils, 1% bands, 1% eosinophils, 2% basophils, 14% lymphocytes; 3% leukocytoid lymphocytes and 3% monocytes. Sedimentation rate was 30 mm/hr. Blood urea nitrogen was 20 mg %. Total cholesterol was 300 mg% and serum triglycerides was 270 mg%. Alkaline phosphatase was 38.5 Bodansky units with a total bilirubin of 6.67 mg%. SGOT was 47 units. Serum protein electrophoresis showed a total protein of 6.6 gm % with albumin, 3.76 gm%; alpha-I globulin - 0.36 gm %; alpha-II globulin - 0.49; beta globulin - 1.01 gm %, and gamma globulin - 0.99 gm %. Immunoglobulins electrophoresis values were: IgM of 166 mg %, IgG - 707 mg%, IgA - 93 mg%, and IgE less than 0.04 mg%. Fasting blood sugar was 100 mg %, and urinalysis was within normal limits. Prothrombin time was 10.0 seconds with a control of 10.5 seconds. The LE preparation remained negative. Chest x-ray was negative.

The retrograde cholangiography was unsuccessful because the catheter could not be introduced into the orifice of the papilla of the duodenum. The dermatologist concluded that the clinical findings and characteristically positive anti-nuclear factor were consistent with the diagnosis of systemic sclerosis. A skin biopsy however showed no pathologic changes of scleroderma and was interpreted as normal.

An exploratory laparotomy to ensure the patency of the common bile duct was recommended. The patient decided to have this done one month later at a local hospital. The surgeon, Dr. H. J. Schmidt, found a slightly enlarged liver with blunted edge but no

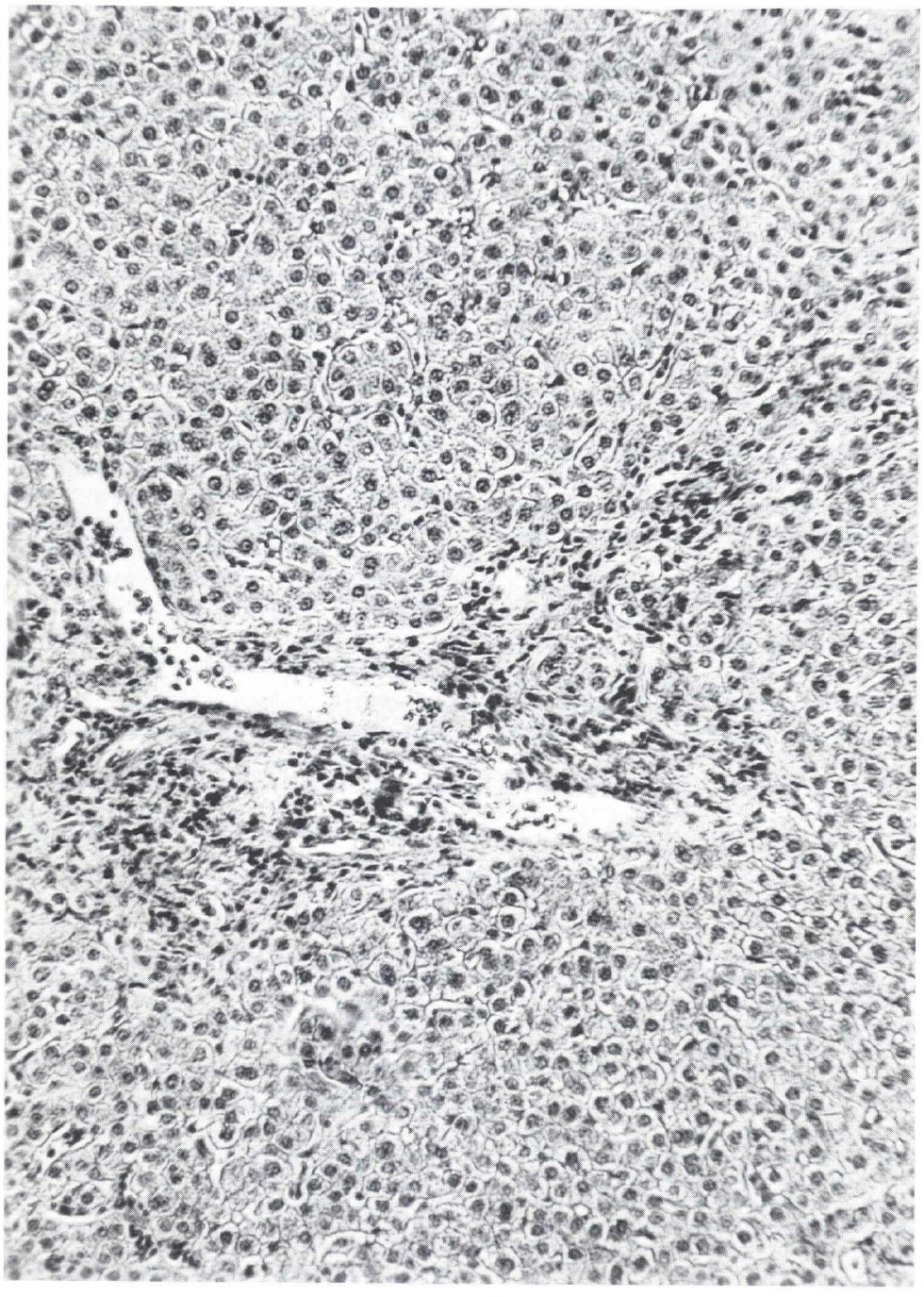

Figure 2

Surgical biopsy of the liver from case II. There is an inflammatory and fibrous reaction in the portal triad. (195x)

nodularity. The gallbladder was normal, and the common bile duct was not enlarged. A cholangiogram demonstrated a normal extrahepatic biliary ststem. Histological examination of a liver biopsy disclosed peri-portal inflammatory and fibrous reaction with bile stasis. The liver biopsy was considered consistent with primary biliary cirrhosis (Figure 2).

Discussion

Systemic sclerosis is well documented in these patients by the finding in both of the typical antinuclear factor pattern of scleroderma and in one patient the striking disorder of esophageal motility. Telangiectasiae similar to Rendu-Osler-Weber syndrome were noted in the first patient. Although both patients exhibited Raynaud's phenomenon, sclerodactyly and calcinosis (to complete the CRST syndrome) were not present.

Biliary cirrhosis has also been well established by classic laboratory findings, including a positive anti-mitochondrial antibody in the first patient, the progressive changes observed in liver biopsies, and the negative exploration of the extra-hepatic biliary tract at the time of cholecystectomy.

Although the occurrence of liver disease in association with scleroderma has been noted since 1934, the close connection between systemic sclerosis and biliary cirrhosis had not been appreciated, according to Murray-Lyon et al.[2] The combination of primary biliary cirrhosis and systemic sclerosis with and without secondary features of calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasiae was first recognized as more than coincidence in 1970 by Reynolds, et al[1] and Murray-Lyon et al.[2]

Case	Age/Sex	Raynaud's Phenomenon	Sclero-dactyly	Calcinosis Cutis	Esophageal Motor Disorder	Telangiectasia			UGI Bleeding
						Hands	Face	GI Tract	
1 (1)	45/F	+	+	+	−	+	+	+	+
2 (1)	50/F	+	+	−	+	+	+	−	+
3 (1)	51/F	+	+	+	+	+	+	+	+
4 (1)	38/F	+	±	+	−	+	−	?	−
5 (1)	51/F	?	−	−	−	+	−	−	−
6 (1)	67/F	±	+	−	−	+	+	?	−
7 (2)	64/F	+	−	−	+	+	+	?	−
8 (2)	60/F	+	+	+	−	+	+	?	−
9 (3)	60/F	−	−	−	−	−	−	−	−
10	48/F	+	−	−	+	−	+	−	−
11	48/F	+	−	−	−	−	−	−	−
Total		9/11	6/11	4/11	4/11	8/11	7/11	2/11	3/11

Table I
Incidence of certain features in 11 patients with biliary cirrhosis and systemic sclerosis.

The present cases represent the tenth and eleventh such patients reported. Although they do not have all the features of the CRST syndrome, as is evident from Table I, neither did six of the previous nine patients.

The presence of granulomas in the portal zones in biliary cirrhosis has been thought to represent evidence for a chronic delayed hypersensitivity reaction to bile duct epithelium or a substance released from it.[7] That such impaired delayed hypersensitivity does indeed exist has been demonstrated in a significant percentage of patients by anergy to skin testing with 2, 4-1 dinitrochlorobenzene and purified protein derivative[8,9]. Other signs of immunologic alteration in biliary cirrhosis are the frequently positive antimitochondrial antibody test, the less frequently positive smooth muscle antibody test, and the abnormal increase of IgM.

Fox et al[11] found that 12 of 33 patients with primary biliary cirrhosis had normal in vitro lymphocyte transformation in response to phytohemagglutinins, but transformation was impaired in the rest of the patients. There was no absolute correlation between transformation and stage of disease, but all patients in the early stages were normal, and those with more advanced disease were impaired.

Analysis of all cases makes it clear that the CRST syndrome may vary in its expression and is not an essential component of the disease combination (Table I). The finding of telangiectasiae of the Rendu-Osler-Weber type in nine cases indicates a possible genetic predisposition.

Systemic sclerosis as a disease of collagen tissue also participates in immunologic misadventures, notably the peculiar anti-nuclear factor pattern of speckled, thready nuclear immunofluorescence, high DRAT titer, and association with "auto-immune diseases" such as systemic lupus erythematosis and rheumatoid arthritis.[10,11] Thus both biliary cirrhosis and scleroderma may share an autoimmune base which may have as its expression one or the other or both diseases. Considerable immunological investigation will be necessary to prove such a connection.

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