Reynolds' syndrome. CREST associated to primary biliary cirrhosis

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Abstract

Reynolds' Syndrome is the association between limited systemic scleroderma (CREST) and primary biliary cirrhosis. We report three patients with this syndrome, emphasizing its main cutaneous characteristics (Dermatol Argent 2008;14(4):276-280).

Key words: *CREST, primary biliary cirrhosis.*

Introduction

Reynolds' syndrome was described in 1971 in relation to the association of CREST-type scleroderma and primary biliary cirrhosis (PBC).[1,2]

Usually, these patients do not show extended forms of scleroderma; they only express sclerodactyly with Raynaud's phenomenon, with scarce facial sclerosis.[3]

Liver involvement manifestations are also oligo-symptomatic, slowly evolving and relatively well tolerated by patients. These circumstances favor the delay of medical consultation.[4,5]

Technological advances allowed for earlier and more precise detection of these patients. For example, the development of Hep-2 cell culture evidences the anti-centromere pattern present in 70 percent of CREST, and the anti-mitochondrial antibody present in more than 80 percent of PBC.[2,6]

Three cases of Reynolds's syndrome patients are shown below.

Clinical cases

Case 1

A 53-year old female, with history of conization for high grade squamous intraepithelial lesion (SIL). She visits the doctor due to the appearance of generalized itching, diffuse cutaneous hyperpigmentation, Raynaud's phenomenon, alopecia, and weight loss.

The physical examination shows fine-drawn nose, facial telangiectasia, salt-and-pepper macules on neckline, chest and back, (**Figures 1** and **2**), scratch lesions, generalized hyperpigmentation, sclerodactyly, scars on fingertips, Raynaud's phenomenon, forearm sclerosis, patchy scar alopecia, hypertrichosis, and earflap chondritis. She refers dry eye and dry mouth.

Laboratory tests: LDH 527 U/l; GOT 52 U/l; GPT 49 U/l; ALP 783 U/l. Protein electrophoresis: normal albumin and

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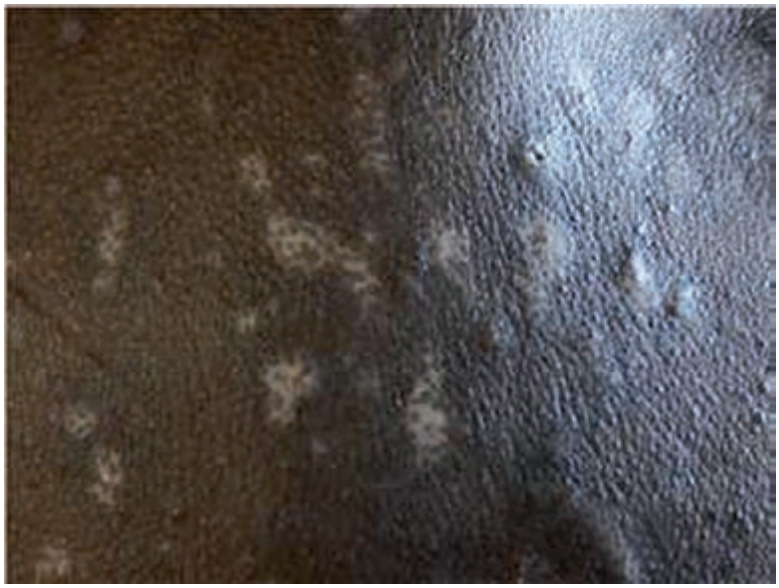

Figure 1. *Salt-and-pepper macules.*

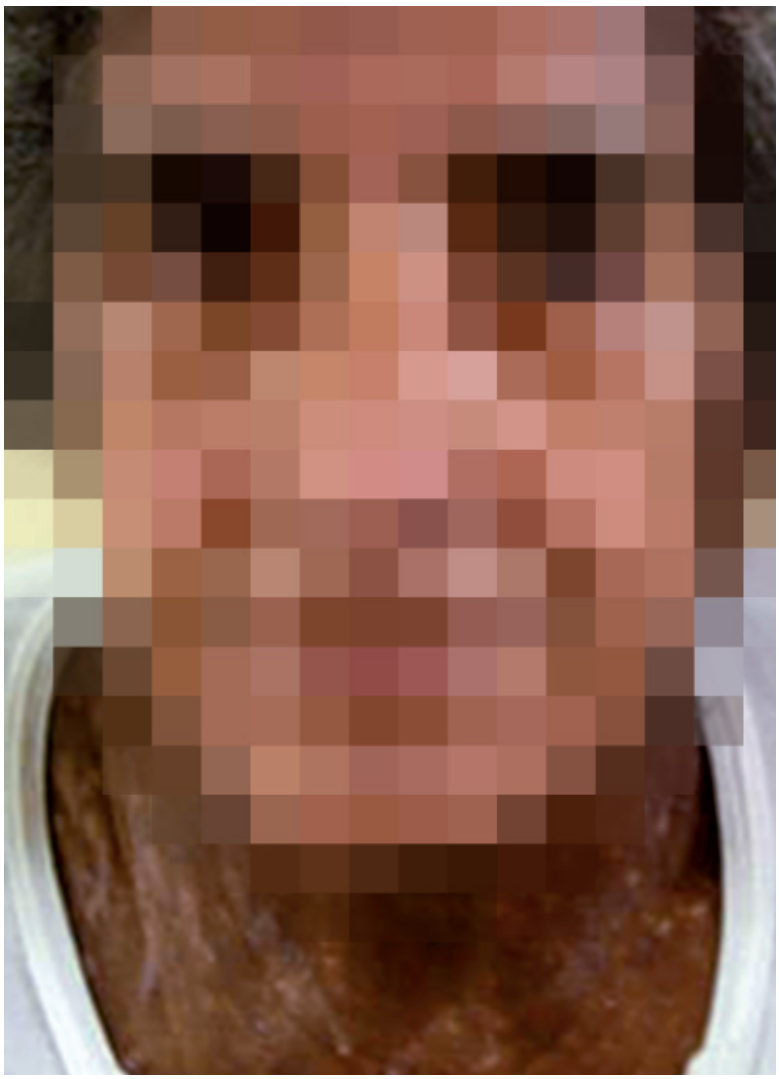

Figure 2. *Fine-drawn nose, generalized hyperpigmentation.*

increase of globulins: alpha-2 0.96 mg/dl (normal range: 0.3-0.7 mg/dl), beta 1.3 mg/dl (n.r.: 0.7-1 mg/dl), gamma 2.43 mg/dl (n.r.: 0.8-1.5 mg/dl).
ESR: 40 mm/h.
Immunologic profile: ANA (+) 1/40 anti-centromere spotted pattern.
Esophagus passage: slow supine position passage, over 1 minute. Peristalsis reduction is observed.
Cholangioresonance: normal extra-hepatic bile pathway.
Capillaroscopy: non-vascular arches in most fingers. Dilation of capillaries. Hemorrhage on right hand.
Bengal Rose Test: positive. Schirmmer's test negative. But 7".
Liver biopsy: liver with signs of pericholangitis and chronic and active cholangitis. Mild to moderate degree of activity. Stage of expansive portal fibrosis with sub-sinusoid extension in acini areas 1 and 3, and total liver volume (Dr. Cravero) consistent with PBC.
Salivary gland biopsy: consistent with Sjögren grade II.
Skin biopsy: reticular dermal sclerosis associated with collagen new-growth consistent with scleroderma (**Figure 3**).
Based on the clinical findings and the laboratory tests, an incomplete CREST diagnose is reached (Raynaud's phenomenon, sclerodactyly, esophagus motility disorders, and telangiectasia) associated to Sjögren, and PBC.

Case 2

Male, 61 years old with family history of liver diseases and personal history of superior and inferior motor neuron disease, positive anti-phospholipid antibodies, and repeatedly mumps. He appears at the physician's office due to left hand index finger digital necrosis and Raynaud's phenomenon of several years' evolution.
Physical examination shows Raynaud's phenomenon, left hand index finger digital necrosis, sclerodactyly (**Figure 4**).
Laboratory tests: GOT 33 U/L, GPT 70 U/L, ALP 450 U/L, ESR 21 mm/h, total proteins 7.7 mg/dl, albumin 3.8 mg/dl, globulin increase, due to gamma-globulin 2.2 mg/dl (n.r.: 0.8-1.5 mg/dl).
Immunologic profile: ANA (HEp 2) 1/80 fine spotted pattern. Anti-centromere (+), Anti CENP B (+), Anti SS-A Ro (+), Anti SS-B/La (+), Ab anti-M2 (+).
Serial esophagus gastroduodenal X-rays: esophagus motility alteration in the lower 2/3 of the esophagus.

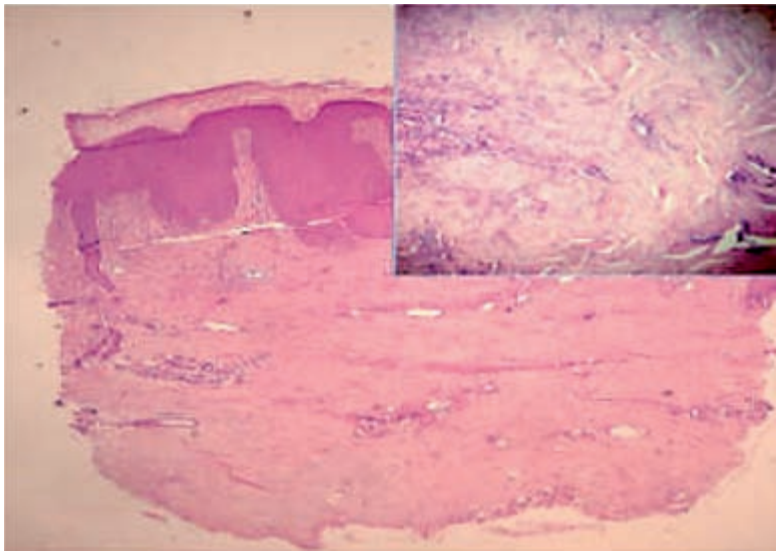

Figure 3. *Reticular dermal sclerosis, consistent with scleroderma (H-E).*

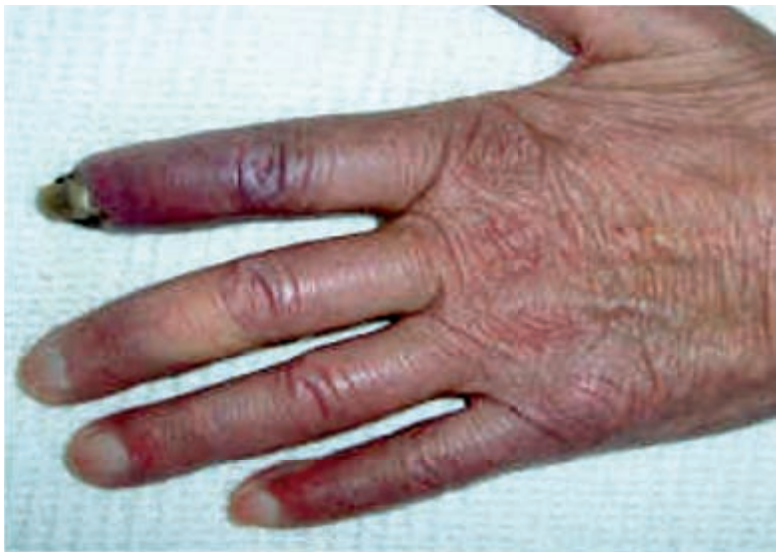

Figure 4. *Left hand index finger necrosis.*

Capillaroscopy: numerous mega capillaries, many non-vascular areas in several fingers and pericuticular hemorrhages forming a scleroderma-like pattern were found in most fields.
Lower lip mucosa biopsy: consistent with Sjögren.
Liver biopsy: excessive iron load, minimal chronic hepatitis with non-specific changes.
Diagnosis: non-specific reactive hepatitis. Consistent with early stages of PBC.
Based on clinical findings, laboratory tests, and histopathology, incomplete CREST is diagnosed (Raynaud's phenomenon, sclerodactyly, and esophagus motility disorders), Sjögren, and PBC.

Case 3

Female, 59 years old. No relevant history. She consults due to Raynaud's phenomenon of several years' evolution, itching of 6 months evolution, digital ulcers and facial telangiectasia of 3 months' evolution.
Physical examination shows telangiectasia on face and neckline, microstomy, angular cheilitis, depapillated tongue, fine-drawn nose, Raynaud's phenomenon, digital ulcers in middle and index fingers of both hands, sclerodactyly, forearm sclerosis. Patient refers dry mouth and eye (**Figures 5** and **6**).
Laboratory tests: GOT 171 U/L, GPT 54 U/L, ALP 1360 U/L, GGT 459 U/L, TB 3.8 mg/dl, DB 2.8 mg/dl. Total proteins 7.1 mg/dl, albumin 2.3 mg/dl, globulin increase: beta 1.04 mg/dl (n.r.: 0.7-1 mg/dl), gamma 3.19 mg/dl (n.r.: 0.8-1.5 mg/dl).
ESR: 73 mm/h.
Serology: HIV, HBV, HVA (-), HCV (+).
Immunologic profile: ANA (-), anti-centromere (-), anti-mitochondria: 1/500, FR 1/80, ANCA (-), Scl 70 (-).
CAT of chest, abdomen, and pelvis: lung fibrosis, ground-glass pattern, bilateral lung nodes, homogeneous hepatomegaly. Enlarged uterus.
Gynecological ultrasonography: Heterogeneous uterus with an image consistent with myoma.
Cholangioresonance: normal extra-hepatic bile pathway.
Capillaroscopy: dilated capillaries, with scleroderma-like pattern.
Esophagus passage: low intensity peristaltic movement, with contrast media remaining longer than normal.
Schirmmer and Bengal Rose tests: positive.
Parotid scintillography: secretion from right parotid below 3 percent, from left parotid 6 percent (normal range: above 40 percent).
Liver biopsy: consistent with PBC stage III. Fibrosis.
Salivary gland biopsy: no evidence of salivary glands.
Skin biopsy: atrophic scleroderma-like appearance associated to marked solar elastosis.
By clinical findings, laboratory test, and histopathology, diagnosis of incomplete CREST is reached (Raynaud's phenomenon, sclerodactyly, esophagus motility disorders, and telangiectasia), Sjögren and PBC.

Comments

Three patients with Reynolds' syndrome (RS) are described: 0/3 with calcinosis, 3/3 with Raynaud's phenomenon, 3/3 with sclerodactyly, 3/3 with esophagus motility disorders, and 2/3 with telangiectasia. The three had associated Sjögren's syndrome. RS is more frequently found in females of about 50

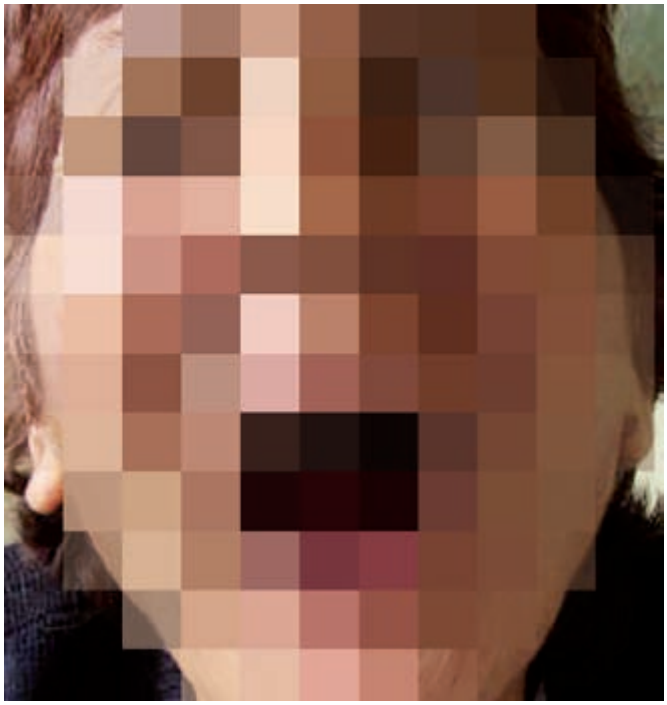

Figure 5. *Microstomy, angular cheilitis.*

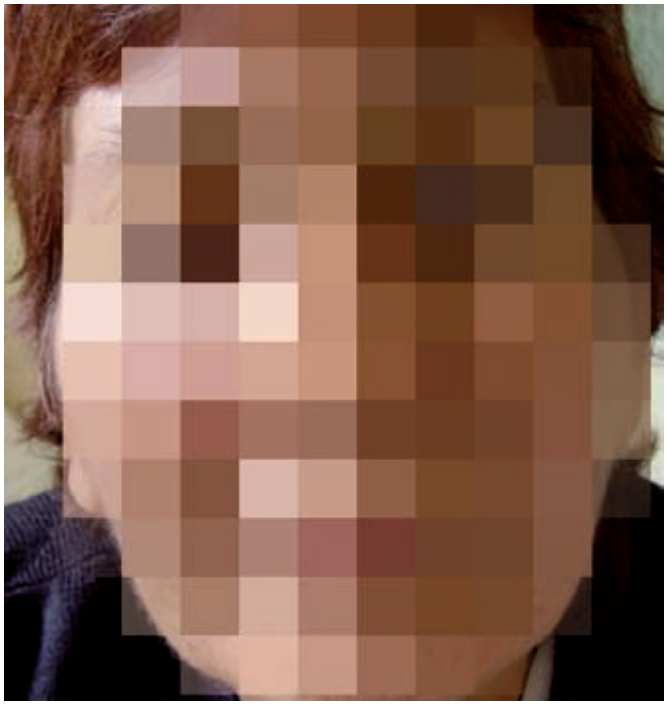

Figure 6. *Fine-drawn nose, telangiectasia.*

years of age. CREST expressions precede in months or years the hepatic manifestations, appearing as incomplete CREST.[6]
It may be associated to pulmonary hypertension exclusive of CREST, due to involvement of the pulmonary artery and its branches.[7]
Skin manifestations of PBC include itching, cutaneous hyperpigmentation excluding mucosa, scratch lesions, xanthoma, and xanthelasma. Laboratory tests show sustained increase of cholestasis enzymes and increase of gamma-globulins (**Table 1**).[2]
In the immunologic profile, 70 percent of the cases evidence ANA (+) with anti-centromere pattern, and in 95 percent of the cases, anti-mitochondrial antibody (+) is found.
In 90 percent of the cases, Reynolds' syndrome is associated with Sjögren's syndrome.[6]
Prognosis of the disease relied on PBC, which has a more benign course in association with scleroderma.[5]
Ursodeoxycholic acid, a bile salts synthesis inhibitor, is suitable for treating PBC, showing alleviation of pruritus and hyperpigmentation; skin sclerosis also improves due to its activity as immunomodulator. The mechanism is currently subject to study.[7,8]

Conclusion

Patients with RS do not present facial sclerosis, or calcinosis. CREST is associated with PBC in 20 percent of the cases. This association may be higher if patients were adequately studied. Association with Sjögren syndrome occurs in 90 percent of the cases.[4,6]

TABLE 1. PBC DIAGNOSTIC CRITERIA.

Diagnostic criteria of PBC (3 of 5)
History of chronic cholestasis.
Increase of ALP 3 times above normal level.
Presence of anti-mitochondrial antibodies.
Serum IgM increase.
Consistent liver biopsy.

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