

Case Report Article

From pruritus to CREST syndrome in a middle aged woman

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Abstract

CREST syndrome, a subtype of scleroderma and Primary Biliary Cholangitis, is an autoimmune disease where the immune system is causing a progressive slow damage to the bile ducts. We report the case of a 67-year-old female patient presenting symptoms indicative of CREST syndrome. During her hospitalization in the internal medicine clinic and after the appropriate imaging and laboratory investigation the diagnosis of CREST syndrome was confirmed, and she was also diagnosed with PBC. This case adds up to a list of literature sources and several case reports which indicate the association of PBC and CREST syndrome, including the accompanied clinical symptoms and musculoskeletal manifestations of the latter.

Keywords: Cholestasis, CREST Syndrome, Liver, PBC, Scleroderma

Introduction

Primary biliary cholangitis is a chronic and slowly progressive autoimmune cholestatic liver disease. Damage is caused to the bile ducts leading to a type of cirrhosis that may eventually lead to liver failure. The primary symptoms are fatigue and pruritus^{1,2}. Primary Biliary Cholangitis was previously known as Primary Biliary Cirrhosis but since cirrhosis occurs in the late stage of the disease this name was inaccurate concerning the patients in the earlier stages. The diagnosis of PBC is based on a combination of clinical findings and abnormal liver function tests. Elevated alkaline phosphatase levels and the presence of antimitochondrial antibodies (AMA) in serum are practically diagnostic^{1,3,4}.

CREST syndrome is a variant of limited scleroderma characterized by calcinosis, Raynaud phenomenon, esophageal motility dysfunction, sclerodactyly and telangiectasia⁵. The three main pathological manifestations of the syndrome include increased collagen deposition, vascular abnormalities and perivascular mononuclear cell infiltration⁶. Women between the age of 30 to 50 are mostly affected. The most common symptoms and complications include: scleroderma mainly affecting the arms and face, dysphagia, and regurgitation due to the esophageal dysmotility. Pulmonary arterial hypertension is the most serious form of lung involvement in CREST syndrome⁷.

According to Wigley et al.⁸ Raynaud's phenomenon is characterized by episodes in which fingers become indolent and cyanotic. These attacks may last from a few minutes to several hours and are triggered by cold or emotional stress.

According to the literature these two pathologies seem to be closely related^{9,10}, not only on their clinical manifestations, since they are both types of fibrotic disease, but also on their laboratory findings and therefore, their diagnostic approach which is based on antibodies (ANA, AMA, ACAs).

Case presentation

A 67 year old Caucasian female presented to the emergency department of our hospital complaining of dysphagia, pruritus and musculoskeletal pain of the arms. The patient also mentioned chronic musculoskeletal pain and acrocyanosis for which she never sought medical attention.

A careful medical history revealed that she suffers from chronic obstructive pulmonary disorder (COPD) due to long-term smoking, and was under treatment for arterial hypertension. The initial clinical examination showed normal blood pressure (115/72 mmHg), normal heart rate (77 bpm), and no pathological findings during auscultation and palpation of the abdomen. The heart and lungs auscultation

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did not reveal any pathological findings. Skin redness was noticed on the site of pruritus.

The blood tests did not reveal any significant findings, however the biochemical test yield findings indicative of disrupted hepatic function (Table 1). Due to these findings, further testing for HBV and HBC were requested, revealing negative results.

A cancer index test was also performed, showing no signs of neoplasia. Thyroid function test (Free T4, TSH) and thyroid ultrasound revealed no pathology as well. A quantitative immunoglobulins test indicated increased levels of IgA, IgM and IgE (Table 2).

A CT scan was performed without intravenous contrast medium due to patient-reported previous allergy. The CT scan did not demonstrate any pathological finding of the liver apart from dilation of intrahepatic bile ducts that was later confirmed sonographically.

Taking into account the pruritus, all the clinical findings and the increased ALP, AST and γ GT levels as well, the possibility of PBC was suggested. So, further specialized tests (ANA and AMA tests) were requested that proved positive (Table 3), thus confirming the diagnosis of PBC.

Due to the persistent musculoskeletal pain in the arms and the sclerodactyly, Anti-centromere antibodies (ACAs) test was conducted which proved positive. During the investigation of the reported dysphagia the patient underwent gastroscopy (Figure 1) that revealed gastritis and esophageal veins dilation¹¹.

Taking into consideration all the pre-mentioned positive findings, the Raynaud phenomenon and the history of acrocyanosis as well, the initial suspicion of CREST syndrome was finally confirmed.

Although, there is cure for PBC, some medications may provide relief of the associated symptoms and decelerate the progression of the disease¹². Our patient was discharged from the hospital's clinic after improvement of her clinical and laboratory status. She was put on treatment with Ursodeoxycholic acid (250mg X 4 per os) to slow down further liver fibrosis, and Colchicine (0,5mg X 2 per os) to lower her bilirubin levels¹³.

For the management of musculoskeletal pain, NSAIDs in ointment form were prescribed, and as far as it concerns the dysphagia, dietary orders were given, like avoiding hot meals and eating earlier in the evening. The prescription of PPIs was not considered necessary in the specific case as the simple dietary orders proved efficient.

For the Raynaud phenomenon and the acrocyanosis the patient was advised to avoid exposure to cold, sudden temperature changes, smoking and stress and she was also prescribed nifedipine, a calcium channel blocker.

Discussion

Primary biliary cirrhosis can be complicated by systematic sclerosis (SSc) and this combination of pathologies has been widely described in literature by a number of books^{3,7},

	Patient values	Reference Range
ALP	798 U/L	42-128 U/L
γ GT	383 U/L	5-45 U/L
AST	50 U/L	4-45 U/L
ALT	49 U/L	4-45 U/L

Table 1. Blood test results, showing elevated levels.

	Patient values	Reference Range
IgA	5,29 (gr/lt)	0,45-3,64 (gr/lt)
IgM	5,29 (gr/lt)	0,03-2,09 (gr/lt)
IgE	23,8 (gr/lt)	5,66-14,25 (gr/lt)

Table 2. Quantitative immunoglobulins test results, clearly positive.

	Patient values	Positive values
ANA	1:1280	titer less than 1:60
AMA	1:2560	titer less than 1:40

Table 3. Autoantibodies liver test results suggestive of both PBC and CREST syndrome.



Figure 1. Images of the gastroscopy, showing signs of gastritis.

studies^{9,14,15} and several case reports¹⁶⁻¹⁸. The complication of PBC with crest syndrome was first reported by Murray-Lyon et al.¹⁹ in 1970. Both PBC and Crest syndrome are autoimmune fibrotic diseases that concern increased levels of pro-fibrotic cytokines, transforming growth factor beta (TGF- β 1) and interleukin 6 (IL-6)²⁰.

Anticentromere antibody (ACAs) has been detected not only in CREST syndrome but also in other autoimmune disorders such as PBC⁴. Higher frequency of Raynaud phenomenon is observed in ACA positive PBC patients than in ACA negative PBC patients, this finding suggests a close association between the presence of ACA and the clinical manifestations of CREST syndrome in PBC patients. Moreover, according to Shoji et al⁴, PBC-CREST patients show lower titers of antiM2 – antibodies (AMA)²¹, and lower levels of total bilirubin than PBC non-Crest patients²².

Concerning Raynaud's phenomenon treatment, a study suggests the prescription of Calcium Chanel Blockers since clinical trials of other substances as endothelin receptor antagonists, osphodiesterase-5 inhibitors, vasodilators, and onabotulinumtoxin A, did not have similar success rates²³. For the management of PBC we prescribed Ursodeoxycholic acid, which according to a plethora of recent articles and studies^{13,24,25} is currently the standard treatment of PBC.

Conclusion

During the treatment of our patient we noticed improvement of the levels of antibodies as well as the liver functions tests such as ALP and IgM titles. Considering the improvement of her overall clinical status, we were lead to the indication that by treating PBC may also help alleviate the CREST syndrome symptoms. PBC can often be complicated by rheumatic diseases^{9,18}, and that is why attending physicians should always consider the possibility of systematic disorder in PBC patient and the vice versa.

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