REVIEW ARTICLE

PACK syndrome: A case series and review

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ABSTRACT

A rare overlap syndrome between CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome and primary biliary cholangitis (PBC) is described as PACK syndrome, an acronym for primary biliary cholangitis, anticentromere antibodies, CREST syndrome, and keratoconjunctivitis sicca. In this retrospective cohort analysis and review, we present fourteen patients who meet diagnostic criteria for PACK syndrome in one of the largest case series of this group. All patients were female, 86% of whom were White with an average age of 66.7 years (range 39-78 years). The prevalence was 5.08% in our PBC cohort (n=256) similar to previous findings. CREST syndrome was diagnosed prior to PBC in 58% of our patients and limited pulmonary and renal involvement were observed. This syndrome is rare, but given its insidious development, clinicians should be aware of this potential overlap in CREST-only and PBC-only patients.

Keywords: PBC; CREST syndrome; PACK syndrome. **[Am J Med Sci 2022;■(■):1–8.]**

INTRODUCTION

Systemic sclerosis (SSc) is a multiorgan autoimmune disorder characterized by small vessel vasculopathy and deposition of extracellular matrix leading to fibrosis and ultimately end-organ dysfunction.[1] SSc can be divided into multiple subsets, including diffuse cutaneous systemic sclerosis (DcSSc), limited cutaneous systemic sclerosis (LcSSc), and systemic sclerosis without skin involvement (SSc *sine* scleroderma).[2] LcSSc and CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) are frequently used interchangeably. For clarity, we will refer to LcSSc and CREST syndrome as the same entity.

What became known as CREST syndrome was described in the medical literature first by Thibièrge and Weissenbach in 1910 and later by Winterbauer in 1964.[3,4] These patients presented with a variation of cutaneous calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. CREST syndrome is now a well-known milder variant of SSc that has been described in association with other autoimmune diseases including primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis.

PBC is a chronic nonsuppurative autoimmune destruction of intrahepatic bile ducts leading to cholestasis and, in some cases, to hepatic cirrhosis. PBC has a predilection for females and is characterized frequently by the presence of antimitochondrial antibody (AMA), which typically precedes the development of clinical disease.[5–7] PBC is also associated with other autoimmune diseases including, most commonly, Sjogren syndrome and Hashimoto thyroiditis.[8–10]

An overlap of CREST syndrome with PBC was first described in two patients by Murray-Lyon and colleagues in 1970 and later expanded upon by Reynolds in 1971.[11,12] This overlap syndrome is now referred to as PACK syndrome, an acronym for primary biliary cholangitis, anticentromere antibodies, CREST syndrome, and keratoconjunctivitis sicca.[13]

Several case series and investigational studies have been published on PACK syndrome since the initial description in 1970. In this paper, we present a new case series of fourteen patients managed at a single academic medical center that expands upon the clinical characteristics, laboratory findings, and the presence of other disorders in PACK syndrome patients. In addition, we review experimental and clinical literature to aid in clinicians' awareness of this syndrome.

METHODS

Patient selection and characteristics

This is a retrospective cohort analysis of patients with CREST syndrome and primary biliary cholangitis (PBC) who were treated at a single academic medical center. After institutional review board approval, patients were selected utilizing the electronic medical record search function. Patient charts were first selected for ICD-10 codes specific for diagnoses of PBC, primary biliary cirrhosis, and primary biliary cholangitis. This search resulted in 256 patients. From this group, charts were screened for ICD-10 codes specific for systemic

sclerosis, CREST syndrome, and limited cutaneous systemic sclerosis. After both filters were applied, eighteen patients carrying both diagnoses in their medical records were found.

These charts were then individually inspected to determine if patients met criteria for systemic sclerosis utilizing the 2013 ACR/EULAR classification criteria and PBC utilizing diagnostic criteria outlined by Lindor and colleagues in the 2018 practice guidance from the American Association for the Study of Liver Diseases.[1,14] Evidence of PBC on liver biopsy was considered the gold standard for diagnosis. However, patients who did not have liver biopsy data available or who had negative biopsies were included if they had reported or documented evidence of elevated alkaline phosphatase level plus positive antimitochondrial antibody.

Patients who did not score ≥9 on the ACR/EULAR classification additionally were considered to have CREST syndrome if they presented with two or more of the known clinical characteristics of the syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) along with positive anticentromere antibody (if available) and abnormal nailfold capillaroscopy. Most patients were diagnosed and treated by rheumatologists and gastroenterologists at the same academic health system. For those who were not, available outside records were independently reviewed during patient inclusion.

Patient characteristics including age, gender, diagnosis, age of onset for both PBC and CREST syndrome, serologies, associated comorbidities, and cause of death (if applicable) were extracted from the medical record and are presented in Table 1. Calcinosis was defined by subcutaneous calcium deposition found on physical exam or imaging. Raynaud phenomenon (RP), defined as color changes in fingers secondary to vasoconstriction, was included based on reported symptoms consistent with RP or classic physical exam findings. Esophageal dysmotility was defined as recurrent episodes of globus sensation or choking and often was confirmed by objective radiographic testing or manometry. Sclerodactyly, skin tightening over the fingers, was included if there was evidence on physical exam. Telangiectasias or vasodilated post-capillary venules were included if >1 was present on physical exam.

Laboratory abnormalities including liver function tests (LFTs) and serology titers were obtained at the date of diagnosis of PBC and CREST syndrome. In cases where either condition was diagnosed prior to referral to our institution or if diagnosis was made prior to electronification of the medical record, the earliest data available was used.

Literature review

To review the latest medical literature, PubMed was queried in March and April 2020. Search criteria were broad to include the various differing nomenclature for the clinical syndromes described above. Search terms included, but were not limited to, CREST, PBC, primary biliary cirrhosis, primary biliary cholangitis, PACK syndrome, and Reynold's syndrome. These search criteria yielded hundreds of articles that were screened for their relevance to patient populations with both PBC and CREST syndrome diagnoses. Multiple studies discussed PBC in association with Systemic Sclerosis in general, and while these were included for completion, they were often not completely applicable to our specific patient population.

RESULTS

After review, a total of fourteen patients met criteria for overlap of CREST syndrome and PBC. All fourteen patients were female with an average age of 66.7 years (range 39-78 years). Two patients were Hispanic and the rest were White. Two patients did not meet the 2013 ACR/EULAR criteria but were included in analysis due to a strong clinical suspicion for CREST syndrome, as one (patient 10) had scleroderma-like microvascular findings on nailfold capillaroscopy, and another (patient 6) had scleroderma diagnosed on esophageal biopsy.

The average age of onset of CREST syndrome was 50.8 years (range 16-74 years). The average duration of CREST syndrome was 15 years. Patients had on average three of the five defining characteristics associated with CREST syndrome at the time of this review. The most frequent characteristic outside the CREST acronym was keratoconjunctivitis sicca found in 13 of 14 patients (93%). Raynaud phenomenon was present in 13 of 14 patients (93%). Data for the age of onset of Raynaud phenomenon was only available for four patients, but developed on average 6.7 years (range 0-21 years) prior to PBC diagnosis and 9.8 years prior to CREST syndrome diagnosis (range 0-28 years). CREST syndrome was diagnosed first in 7 of 12 patients for which data were available.

The prevalence of PACK syndrome in our cohort of PBC patients (n=256) was 5.08%. The average age of onset of PBC was 55 years (range 32-69 years). Thirteen patients underwent liver biopsy, with eleven showing evidence of PBC. Of the remaining two patients, one had negative histology for PBC and one had no available records from the procedure. Both patients were included due to history of positive AMA and elevated alkaline phosphatase. Further details regarding the grade of inflammation and stage of fibrosis utilizing the Ludwig and Scheuer systems can be found in Table 1. The average alkaline phosphatase and total bilirubin levels on diagnosis were 225.3 U/L and 0.74 U/L, respectively. The average aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels on diagnosis of PBC were 45.8 U/L and 49.4 U/L, respectively.

All patients with available results were antinuclear antibody (ANA) positive, with titers ranging from 1:320 to 1:10,240. Eleven patients were anticentromere antibody

Table 1. Characteristics of 14 female patients with PACK syndrome.

Pt#	Primary Biliary Cholangitis							CREST Syndrome									
	Age of onset	Alk Phos*	T. Bili*	AST*	ALT*	AMA*	Liver bx*	Histology**	Age of onset	Calcinosis	Raynaud Phenomenon	Esophageal Dysmotility	Sclerodactyly	Telangiectasia	ACA*	KCS*	Meets 2013 ACR/EULAR Criteria
1	47	432	1.3	36	53	+^	+	Grade 2 Stage 0	48	-^	+	+	-	-	+	+	Yes
2	69	83	0.3	91	113	+	n/a^	n/a	39	+	+	-	+	+	+	+	Yes
3	63	105	1	23	24	+	+	Grade 2 Stage 1	67	-	+	+	-	+	+	+	Yes
4	67	355	0.4	38	23	+	-	Stage 0	55	+	+	-	+	+	n/a	-	Yes
5	66	400	0.4	83	64	-	+	Grade 1 Stage 1	43	+	+	-	+	+	+	+	Yes
6	58	225	0.6	38	43	+	+	Grade 2 Stage 2	35	-	+	+	-	-	n/a	+	No
7	32	172	1	42	49	n/a	+	Grade 2 Stage 2	16	-	+	+	+	+	-	+	Yes
8	52	176	1.1	47	43	+	+	Grade 1 Stage 1	59	+	+	+	+	+	+	+	Yes
9	n/a	140	0.4	22	24	n/a	+	Grade 2 Stage 2	n/a	-	+	+	+	+	+	+	Yes
10	37	308	0.7	48	74	+	+	n/a	37	-	-	-	-	-	+	+	No
11	56	301	0.8	50	43	n/a	+	n/a	74	-	+	+	-	+	+	+	Yes
12	55	198	0.6	53	55	n/a	+	Grade 1 Stage 1-2	65	-	+	-	+	+	+	+	Yes
13	n/a	168	1	23	30	+	+	n/a	67	-	+	-	+	+	+	+	Yes
14	58	91	0.8	47	53	+	n/a	n/a	56	+	+	+	-	+	+	+	Yes

* Alk Phos, alkaline phosphatase (normal range 35-150 U/L); T. Bili, total bilirubin (normal range 0.2-1.2 mg/dL); AST, aspartate aminotransferase (normal range 5.0-34 U/L); ALT, alanine aminotransferase (normal range 5.0-45 U/L); AMA, antimitochondrial antibody; Liver bx, Liver Biopsy; ACA, anticentromere antibody; KCS, keratoconjunctivitis sicca; ACR/EULAR, American College of Rheumatology, European Union League Against Rheumatism classification criteria score for systemic sclerosis.

** Liver biopsy histology grades of inflammation and stage of fibrosis using Ludwig and Scheuer systems.

^ + Positive; - Negative; n/a, not available.

Table 2. Autoantibodies detected in current series of PACK syndrome patients.

Patient Number	ANA*	ANA pattern	AMA*	SS-A/Ro*	SS-B/La*	SCL-70*
1	1:2560	Centromere	+^	-^	-	-
2	1:320	Centromere	+	n/a^	n/a	-
3	1:640	Centromere	+	+	n/a	n/a
4	n/a	n/a	+	n/a	n/a	n/a
5	1:2560	Centromere	-	-	-	-
6	1:2560	Speckled	+	+	-	-
7	1:320	Nucleolar	n/a	n/a	n/a	-
8	1:1280	Centromere	+	+	-	-
9	1:640	Centromere	n/a	-	-	-
10	1:1280	Centromere	+	-	-	-
11	1:2560	Centromere	n/a	+	-	-
12	1:10,240	Centromere	n/a	+	-	-
13	1:2560	Centromere	+	n/a	n/a	-
14	1:2560	Centromere	+	-	-	-

* ANA, antinuclear antibody titer; AMA, antimitochondrial antibody; SS-A/Ro, Sjogren syndrome antibody A or anti-Ro antibody; Sjogren syndrome antibody B or anti-La antibody; SCL-70, or topoisomerase I antibody.
^ + Positive; - Negative; n/a, not available.

(ACA) positive (79%), and nine were AMA positive (64%). Of the remaining five patients, four had no available AMA testing results and one tested negative. Interestingly, the AMA-negative patient had evidence of PBC on liver biopsy. The most common serology other than ACA and AMA was Sjogren syndrome antibody-A (SS-A), found in five patients (36%). Testing for antibodies directed against other extractable nuclear antigens (ENA) and other serologies like rheumatoid factor were inconsistent among patients. Data were extremely limited for antibodies associated with other subsets of SSc like anti-topoisomerase I (SCL-70) and RNA polymerase III antibody. Only two patients were tested for RNA polymerase III and both were found to be negative. All patients tested for SCL-70 were negative. The compiled serology results can be found in Table 2.

Additional overlapping rheumatologic disorders were also noted. The most common disorder was Sjogren syndrome, found in five patients (36%). Rheumatoid arthritis was present in one patient. Dermatomyositis was diagnosed in one patient in association with a new malignancy during the study.

Other medical conditions in our cohort included hypothyroidism in seven patients (50%), heart failure with preserved ejection fracture in four patients, interstitial lung disease in three patients, pulmonary arterial hypertension in two patients, and gastroesophageal reflux disease found in thirteen patients. There were two patients with chronic kidney disease. Complications from longstanding CREST and PBC were rare and included two patients with compensated cirrhosis and one patient with decompensated cirrhosis requiring liver transplant. Portal hypertension was seen in two individuals. One patient developed small bowel pseudo-obstruction from CREST syndrome. A comprehensive list of complications along with treatments are described in more detail in Table 3.

DISCUSSION

PACK syndrome is a rare autoimmune overlap syndrome comprised of CREST syndrome and PBC that was first described by Murray-Lyon and colleagues in 1970 and later expanded upon by Reynolds in 1971.[11,12] Over the last five decades, more research and cohort studies have been performed to accurately define this syndrome and its characteristics. A summary of previous case reports along with the current case series is given in Table 4.[5,10,15,11–13,16–20]

PACK syndrome primarily affects White females in the fourth to fifth decade of life.[13,21–23] It has also been described in males, though rarely.[15] This was affirmed by our case series in which 86% were White females who developed both PBC and CREST syndrome on average around age fifty. The prevalence of PACK syndrome in PBC-only or CREST-only populations is highly variable, ranging from 2% to 22%, in part due to varying definitions of what constitutes CREST syndrome and recent changes in classification criteria for SSc.[5,13,22,24–30] Our prevalence of PACK syndrome in our PBC-only cohort was consistent at 5.08%.

Phenotypic expression of PACK syndrome is similar to PBC or CREST syndrome occurring alone except for an increased frequency of calcinosis and telangiectasia. Differences in frequency of digital pitting, lung fibrosis, and esophageal dysmotility have also been observed, though these were not statistically significant.[21] In several studies, symptoms of SSc, most commonly Raynaud phenomenon, presented prior to the diagnosis of PBC.[13,21,23,25] Fifty-eight percent of our cohort was diagnosed with CREST syndrome prior to their hepatobiliary disease, similar to the fifty-nine percent encountered in a large Spanish cohort.[22] In our series, CREST syndrome was diagnosed on average fifteen years prior to PBC with Raynaud phenomenon preceding CREST syndrome by 6.7 years. Rarely,

Table 3. Treatments and complications of 14 PACK syndrome patients.

Patient #	CREST Treatment*	PBC Treatment*	CREST Complications**	PBC Complications**
1	HCQ	UDCA	None	Pruritus
2	AML, OMP	None	None	Pruritus
3	HCQ, OMP, FMT	UDCA	ILD	None
4	TDL, DILT, NTG	UDCA^	PAH, ILD, CP, DU	Pruritus
5	OMP, PC, PRED	UDCA, HXY	DU	Pruritus
6	HCQ, OMP	UDCA, HXY, NLTX	ILD,SE	Pruritus
7	FMT	UDCA, RFP, CC	None	CLC, pruritus
8	OMP, IVIG	UDCA	None	CLC
9	OMP	UDCA	None	None
10	None	UDCA	None	None
11	NFD, NTG	UDCA, HXY	DU	DLC, liver tx, PH, pruritus
12	HCQ, PC	UDCA	SBPO	CLC, PH
13	AML	UDCA	None	None
14	AML, PPZ, NTG	UDCA	None	Pruritus

* HCQ, hydroxychloroquine; UDCA, ursodiol; AML, amlodipine; OMP, omeprazole; FMT, famotidine; TDL, tadalafil; DILT, diltiazem; NTG, nitroglycerine ointment; PC, pilocarpine; PRED, prednisone; HXY, hydroxyzine; NLTX, naltrexone; RFP, rifampin; CC, colchicine; IVIG, intravenous immunoglobulin; NFD, nifedipine; PPZ, pantoprazole.

** ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; CP, cor pulmonale; DU, digital ulcerations; SE, scleroderma esophagus; CLC, compensated liver cirrhosis; DLC, decompensated liver cirrhosis; liver tx, liver transplant; PH, portal hypertension; SBPO, small bowel pseudo-obstruction.

^ Patient 4 was intolerant to ursodiol, and this was discontinued.

a severe necrotizing vasculitis has developed in patients with CREST syndrome overlapping with other autoimmune diseases, and clinicians should be aware of its possible development in PACK syndrome patients.[31–33] This may be linked to ACA positivity, as more severe peripheral vascular disease was seen when compared with other scleroderma associated antibodies.[34] ACA positivity is also highly specific for the development of CREST syndrome features in PBC patients and regular screening for AMA in SSc patients and ACA in PBC patients is now being suggested.[35–40]

ACA positivity may also play a protective role in PACK syndrome patients. This was explored by McCarty and colleagues, who found that ACA positivity was associated with significantly reduced major organ involvement in CREST syndrome when compared to other subsets of scleroderma.[41] More recently, studies exploring ACA positivity in PACK syndrome have discovered significant lower activity of PBC by laboratory evidence and an overall better prognosis when compared to ACA negative patients.[36] Baseline alkaline phosphatase levels may be higher, however.[28]

Because of this milder presentation, less aggressive treatments may be needed. We noted very few complications from long standing disease in our cohort which included only three patients with cirrhosis, two patients with portal hypertension, three patients with interstitial lung disease, and one patient with small bowel pseudo-obstruction. Treatment in most of our patients was focused primarily on symptom relief with proton pump inhibitors and calcium channel blockers for their CREST syndrome, and ursodiol for their PBC.

This milder presentation should not detract from the overall increased mortality in PACK syndrome compared to the general population, which is primarily attributed to increased incidence of pulmonary fibrosis, pulmonary arterial hypertension, and cardiac conditions.[42,43] When the mortality of PACK syndrome patients was compared to PBC patients, no difference in overall survival was noted. However, there was a slower rate of progression of liver disease, slower rate of bilirubin increase, and overall lower rate of liver transplant requirement.[20,44] The mortality rate is higher for PACK syndrome patients when compared to other subsets of scleroderma overlapping with PBC, but this was attributed to non-scleroderma related causes and cumulative survival based on Kaplan-Meyer curves, which was not significantly different.[22]

There are several limitations of our study mostly stemming from its design as a retrospective analysis. Our data on both development of symptoms and diagnosis are likely confounded by the ability of patients to obtain access to subspecialists and to healthcare in general. In some cases, laboratory and biopsy data were missing from the time of diagnosis, and therefore the earliest available data were then included. We acknowledge that this may lead to slight inaccurate representation of some of the data, however, a high variability from their true value is unlikely. ICD-10 codes in the EMR are often out of date or inaccurate. Because of this, we cannot guarantee that all patients with PACK syndrome were captured during the initial inclusion. Future studies with larger sample sizes and more patient follow up are needed.

Table 4. Summary of previous PACK syndrome case reports.

Author	Date of publication	Study type	Location	# of PBC/SSc patients*	Summary
Bartholomew et al[19]	1964	Retro- cohort	USA	2	Cohort included 727 patients. 8 patients with systemic sclerosis and liver disease. 2 cases with likely CREST and unconfirmed PBC. Systemic sclerosis presented years prior to development of liver disease in these patients.
Murray-Lyon et al[11]	1970	Case series	UK	2	Case 1 with systemic sclerosis and stage 2 PBC. Case 2 with CREST and stage 1 PBC. First case series to describe overlap syndrome of CREST and PBC.
Reynolds et al [12]	1971	Case series	USA	6	All female patients with diagnostic criteria consistent with PBC and varying features of CREST syndrome. This is the second case series suggesting an immunologic link between the two syndromes.
O'Brien et al[18]	1972	Case report	USA	1	First case describing systemic sclerosis without features of CREST syndrome overlapping with PBC.
Sherlock and Scheuer[5]	1973	Case series	UK	3	100 patients with PBC were described. 3 patients were found to have CREST syndrome for a calculated incidence of 3%. CREST syndrome was not the presenting feature in these three patients.
Okano et al[17]	1984	Case report	Japan	1	58-year-old female developed CREST syndrome and PBC 20 years following silicone injections. Multiple serologies were positive along with biopsy proven systemic sclerosis, PBC, and positive Schirmer's test. Patient had HLA-DR2 and HLA-DR9 which genetically predisposed her to CREST and PBC. This case describes silicone as possibly facilitating the development of CREST/PBC.
Powel et al[13]	1987	Case series	USA	22	22 patients with CREST syndrome and PBC out of 558 total PBC patients for an incidence of 3.9%. All were female. Majority of patients had scleroderma symptoms prior to PBC (59%). Morbidity and mortality related primarily to liver disease. ACA was present in all patients. Keratoconjunctivitis sicca in 91%.
Launay et al[16]	1998	Case series	France	8	8 patients with systemic sclerosis, PBC, and Sjogren's syndrome. 5 patients had labial salivary gland biopsies that were positive for histological evidence of all three syndromes. Salivary gland biopsy potentially could be used to diagnose these conditions.
Kouraklis et al[15]	2002	Case report	Greece	1	69-year-old male with CREST syndrome developed biopsy proven PBC 14 years after CREST diagnosis. Suspected first case report of PACK syndrome found in a male in English language publications.
Stadie et al[20]	2002	Case series	Germany	2	Raynaud phenomenon can be an early clinical manifestation of PACK syndrome. PBC/SSC overlap has slower progression of PBC
Nakamura et al[10]	2007	Case series	Japan	2	Two Japanese women diagnosed with incomplete CREST syndrome and PBC. Case 1 complicated by Hashimoto Thyroiditis and Sjogren's. Case 2 complicated by Graves and Sjogren's. Both patients were HLA-DR4 and HLA- DR8 positive suggesting a linkage between the four syndromes. Clinical symptoms of CREST syndrome were mild in the setting of PBC.
Collins et al	2023	Case series	USA	14	14 patients meeting diagnostic criteria for PACK syndrome. Their characteristics were described. This is one of the largest case series of PACK syndrome patients.

* Number of patients with overlapping primary biliary cholangitis (PBC) and systemic sclerosis (SSc)

CONCLUSIONS

The overlap of the CREST syndrome and primary biliary cholangitis (PBC) is now known as PACK Syndrome, an acronym for primary biliary cholangitis, anticentromere antibodies, CREST syndrome, and keratoconjunctivitis sicca. We have reviewed the latest literature and presented fourteen additional cases of PACK syndrome treated at a single academic medical center.

This syndrome is rare, however given the insidious development in patients with either CREST syndrome or PBC alone, clinicians should be aware of this potential overlap and perform adequate screening.

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DECLARATION OF CONFLICTING INTEREST

The Authors declare that there is no conflict of interest.

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