Case Report

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Epigastric discomfort in a young woman: unveiling a case of CREST syndrome

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Introduction and Importance: CREST syndrome is a clinical condition seen in relation to systemic sclerosis, which meets at least three of its five clinical features: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Three of these clinical features (Raynaud's phenomenon, sclerodactyly, and esophageal dysmotility) are often present in classical subsets of SSc: limited and diffuse, and their presence alone in association does not define CREST syndrome. Laboratory findings (autoimmunity) are crucial for diagnosis. Hence, a comprehensive clinical assessment and autoimmune investigations should be performed to make the final diagnosis of CREST Syndrome, as per the criteria stated. We describe a case involving a 34-year-old female who was diagnosed with CREST Syndrome during a medical evaluation of her epigastric discomfort.

Case Presentation: We present the case of a 34-year-old female who presented with clinical cutaneous and gastrointestinal manifestations along with autoantibody production when investigated, which was compatible with the diagnosis of a limited form of systemic sclerosis (SSc), CREST syndrome.

Clinical Discussion: In the absence of a diagnostic test to prove the absence or presence of SSc, the diagnosis is based on a combination of clinical and laboratory findings. Thus, a detailed clinical history and careful physical examination are required. With regard to the diagnosis, an updated classification criteria for SSc, as published by ACR/EULAR in 2013, is used and helped us to reach the final diagnosis.

Conclusion: CREST syndrome, a rare clinical entity, warrants consideration by primary physicians while evaluating it. Despite its rarity, inclusion in differentials is essential to prevent the worsening of the condition and further complications. Heightened awareness among healthcare providers is pivotal for prompt recognition and appropriate management.

Keywords: anti-centromere antibody, autoimmunity, case report, CREST syndrome, sclerodactyly, systemic sclerosis (SSc)

Introduction

CREST syndrome is a limited form of systemic sclerosis that has been described as a form of progressive systemic sclerosis in which there is relatively limited involvement of the skin, prominence of calcinosis, Raynaud's phenomenon, esophageal dysmotility, and telangiectasia[1].

The acronym *CREST* was coined in 1964 by Winterbauer in the USA, but the first case report was by French physicians Thibierge and Weissenbach in 1910, which stands for:

(1) Calcinosis cutis – is a deposition of insoluble calcium in the skin and subcutaneous tissues.
(2) *R*aynaud phenomenon.
(3) *E*sophageal dysmotility – due to fibrosis of the distal oesophagus. It manifests as symptoms of gastroesophageal reflux (heartburn and regurgitation).
(4) *S*clerodactyly – thickening of the skin of the hands and feet. It begins as a non-pitting oedema of the hands and fingers. Later, in the course of the disease, the skin becomes thickened, tight, and shiny. Thinning of the skin (atrophy) follows.
(5) *T*elangiectasia.

HIGHLIGHTS

- In the absence of a diagnostic test to prove the absence or presence of systemic sclerosis, the diagnosis was based on a combination of clinical and laboratory findings.
- Although CREST syndrome is a rare clinical entity, it warrants consideration by primary physicians while evaluating it.
- Heightened awareness among healthcare providers is pivotal for prompt recognition and appropriate management of the CREST syndrome.
- This case also adds valuable insights to the rare cases of CREST syndrome, underlining the necessity to advocate further research into this autoimmune connective tissue disorder.

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The apparent increase in both the incidence and prevalence over the last 50 years is most likely due to improved classification, earlier diagnosis, and survival. The SSc diagnosis was reported to occur at the ages of 33.5–59.8 years in Europe and 46.1–49.1 years in North America, and to occur more commonly in women (female:male ratio of 3.8–11.5:1 in Europe and 4.6–15:1 in North America). Women have continuously greater prevalence and incidence rates, indicating a clinically significant difference in the occurrence of SSc across sexes[2]. This case also reports an individual female who has been recently diagnosed with CREST syndrome. CREST syndrome may account for 22–25% of all occurrences of systemic sclerosis, according to serum antibody investigations; however, epidemiologic research specifically looking at CREST syndrome is missing[3]. Three of these clinical features (Raynaud's phenomenon, sclerodactyly, and esophageal dysmotility) are often present in classical subsets of SSc: limited and diffuse. Calcinosis appears to be less common in SSc, and its association with other clinical features is characteristic of CREST syndrome. Therefore, it can be appreciated that calcinosis is the key element of CREST syndrome[4].

Although the exact cause of CREST syndrome is still unknown, it is thought to be the result of a complex interplay of genetic, immunological, and environmental variables depicting multigenic/multifactorial causes.

We report the case of a 34-year-old female who presented with clinical cutaneous and gastrointestinal manifestations along with autoantibody production when investigated, which was compatible with the diagnosis of a limited form of systemic sclerosis (SSc), CREST syndrome.

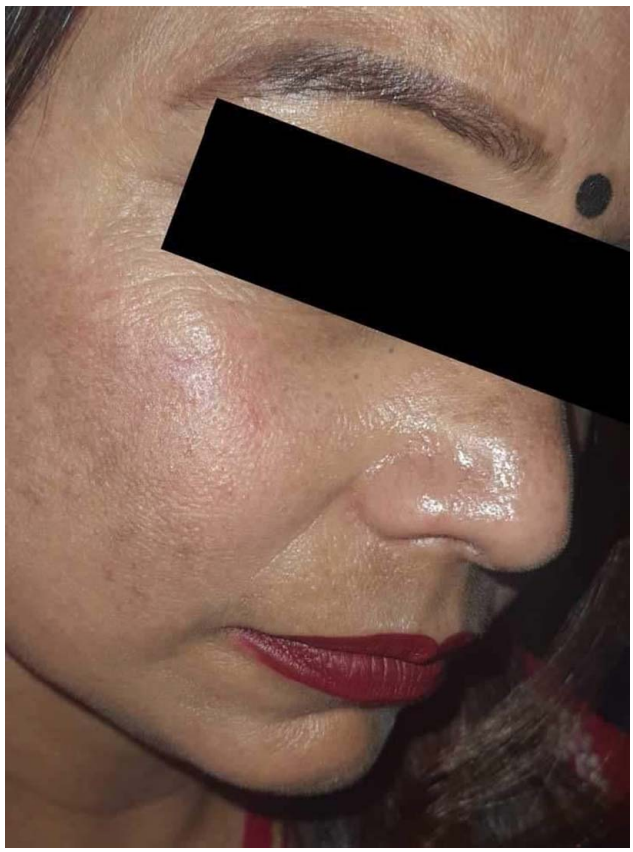

Figure 1. A female patient is exhibiting *telangiectasia* over her right cheek.

Case presentation

A 34-year non-alcoholic, non-smoker female with no known personal or family history of any autoimmune disease presented to the outpatient department (OPD) with epigastric pain for 6 months, which was on and off in nature, gradual in onset, burning type, relieved by proton pump inhibitors and associated with frequent nausea, belching, and early satiety. She underwent endoscopy on multiple occasions with inconclusive findings. There was a matted superficial dilation of capillaries ~1 × 1 mm in dimension, suggesting telangiectasia (see Fig. 1) over her right cheek. She also had a history of Raynaud's phenomenon over time, exhibiting triphasic colour changes in the digits of her hands (see Fig. 2), which she admits to finger colour change with temperature alteration and skin tightening on the hands. She complained of loss of appetite, nausea, and weakness for approximately a month. There was no history of fever, palpitations, vomiting, cough, hematemesis, or hemoptysis. The patient had a normal sleep rhythm, spending 8 h in bed each night to allow at least 7 h of sleep. Her bowel and bladder habits are normal. There was no history of DM, hypertension, asthma, or blood transfusion. The patient had no history of altered sensory function. She denied any history of meningitis, tuberculosis, metabolic disorders, jaundice, malaria, or any central nervous system infections. She is a housemaker by profession, non-vegetarian by diet, and has a mid-level socioeconomic status.

For clinical assessment, she was thoroughly examined for her presenting complaints. On general examination, the patient was conscious, cooperative, and well-oriented to time, place, and person, sitting on a chair, though looking ill and a bit anxious, and she was well built. Her vital signs were stable with a respiratory rate of 27 breaths/min, which was regular and thoracoabdominal; her PILCCOD (pallor, icterus, lymphadenopathy, clubbing, cyanosis, oedema, dehydration) examinations were nil. Following this, a routine systemic examination was performed, which revealed bilateral equal air entry with no addition; S1 and S2 heart sounds were easily appreciated with no murmur. Examination of the gastrointestinal system revealed that her abdomen was flat, the skin over the abdomen was smooth and shiny, and the umbilicus was central and inverted with a transverse slit. All quadrants moved equally during respiration. There was no pigmentation or venous prominence, and the hernial sites were intact. However, on superficial palpation of her abdomen, there was no increase in temperature or tenderness, but she had increased abdominal girth with no organomegaly on deep palpation. There were no signs of guarding or rigidity, whereas on percussion, there was a tympanic sound all over the abdomen with no fluid thrill and shifting dullness, and two to three bowel sounds were heard per minute on auscultation. On examination of her central nervous system, her mental function and cranial nerves were intact, and her pupils were equal and bilaterally reactive to light. On further physical evaluation, sclerodactyly (see Fig. 2) was clinically evident in her hands. She had localised digital skin thickening, which was non-pitting type, consistent with systemic sclerosis, an autoimmune disease characterised by widespread fibrosis of multiple organ systems, swelling of the fingers, and mild pruritus, but there was no evidence of calcinosis in our case. Studies have also shown that more than half of the

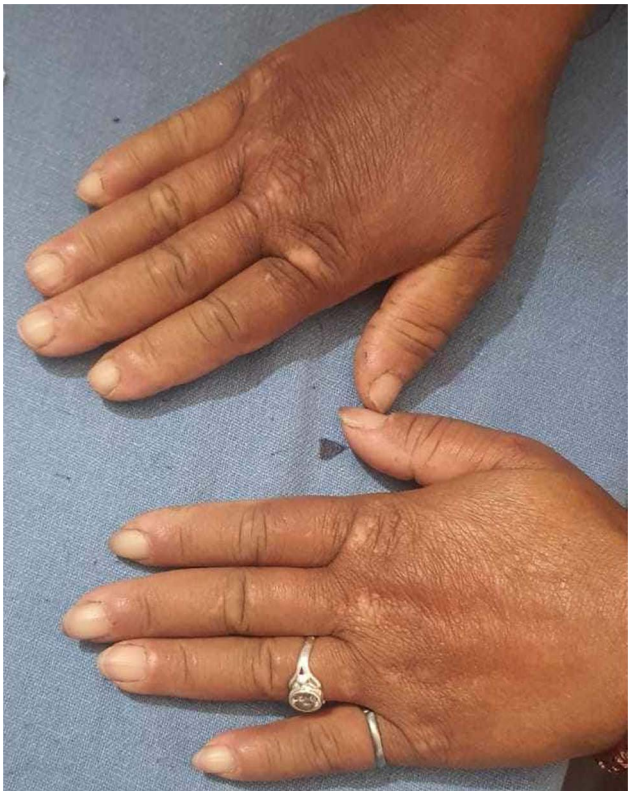

Figure 2. Bilateral signs of *Raynaud phenomenon* in a patient's hands. The patient is exhibiting triphasic colour changes in the digits of her hands, indicative of the Raynaud phenomenon along with *sclerodactyly*.

CREST syndrome cases have elevated titers of anti-centromere antibodies[5]. Therefore, following a comprehensive clinical assessment, autoimmune investigations were performed. Initially, a positive result was obtained for antinuclear antibody (ANA) [325.0 AU/ml; $N < 40$]. Positive ANA tests are the possible signs of various autoimmune diseases, such as lupus, scleroderma, Sjögren's syndrome, juvenile arthritis, or polymyositis and dermatomyositis. Thus, based on her clinical presentation, subsequently, a whole autoimmune panel including an anti-centromere antibody test was conducted, yielding positive findings [Centromere A: 152.0 RU/ml and Centromere B: 153 RU/ml; $N < 5.0$] and eliminating all other possible diagnostic impressions (of autoimmune disorders) except for scleroderma. Table 1 shows the patient's laboratory findings during her last visit.

Hence, in this case, we had *11 scores* (demonstrated in Table 2) supporting the diagnostic impression of CREST syndrome according to the ACR/EULAR criteria, as mentioned above.

After being diagnosed with CREST syndrome, she was advised to have (1) lifestyle modification, which includes head elevation while sleeping, excluding triggering food/substance abuse, consuming small/frequent meals during the day and (2) a prescription for proton pump inhibitors (PPIs) for gastrointestinal manifestations. Along with these conservative measures, she was managed with low-dose steroids for her presenting symptoms, advised to undergo physical therapy and exercise to relieve her discomfort, and, finally, she was referred to a rheumatologist.

Table 1

Autoimmune investigations of the patient during her last consultation visit.

Immunology panel	Patient's results	Reference values
ANA	325 AU/ml	< 40
dsDNA Ab (CLIA)	3.62 IU/ml	< 30
ENA/ANA Profile 23 (IgG)		
Centromere A	152.0 RU/ml	< 5
Centromere B	153.0 RU/ml	< 5
dsDNA	0.0 RU/ml	< 5
Nucleosome	2.0 RU/ml	< 5
Histones	0.0 RU/ml	< 5
SS-A	0.0 RU/ml	< 5
Ro-52	3.0 RU/ml	< 5
SS-B	1.0 RU/ml	< 5
RNP/Sm	0.0 RU/ml	< 5
Sm	1.0 RU/ml	< 5
PM-Scl100	0.0 RU/ml	< 5
PM-Scl75	3.0 RU/ml	< 5
RP11	3.0 RU/ml	< 5
RP155	2.0 RU/ml	< 5

Bold signifies above normal value.

Clinical discussion

In the absence of a diagnostic test to prove the absence or presence of SSc, the diagnosis is based on a combination of clinical and laboratory findings. Thus, a detailed clinical history and careful physical examination are required. With regard to the diagnosis, an updated classification criteria for SSc, as published by ACR/EULAR in 2013[6], is used and helped us to reach the final diagnosis. The criteria states,

Major criteria:

(1) Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (MCP) is sufficient to classify a subject as having an SSc;
(2) Skin thickening sparing the fingers' is classified as not having SSc.

Minor criteria:

(1) Skin thickening of the fingers – puffy fingers and sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints);
(2) Fingertip lesions – digital tip ulcers and fingertip pitting scars;
(3) Telangiectasia;
(4) Abnormal nailfold capillaries;
(5) Pulmonary arterial hypertension and/or interstitial lung disease;
(6) Raynaud's phenomenon;
(7) SSc-related autoantibodies:
    (i) Anti-centromere,

Table 2

Diagnostic scoring of the patient's clinical findings.

Clinical findings	Score
Sclerodactyly	4
Telangiectasia	2
SSc-specific antinuclear antibody – anti-centromere	3
Raynaud's phenomenon	2
Total	11 points

Table 3

Depicting diagnostic criteria (scoring) for SSc.

Diagnostic criteria	Score
Skin sclerosis/thickening of the fingers proximal to the metacarpophalangeal joints	9
Sclerodactyly or digital oedema	4/3
Fingertip pulp ulcers or stellate scars	2/3
Telangiectasia	2
Abnormal capillaries	2
Lung fibrosis	2
Lung arterial hypertension	2
SSc-specific antinuclear antibodies Anti-centromere Anti-Scl-70 Anti-RNA polymerase III	3
Raynaud's phenomena	2

(ii) Anti-topoisomerase I [anti-Scl-70],
(iii) Anti-RNA polymerase III.

The above-mentioned criteria have been assigned a unique score for each individual clinical feature, which is depicted in Table 3 below.

Using this scoring system, *a score of 9 or higher* indicates the classification of systemic sclerosis. Furthermore, gastrointestinal involvement is universal in systemic sclerosis. The symptoms can range from mild to severe, and any segment of the gastrointestinal tract may be affected. The lower esophageal sphincter becomes hypotonic and exacerbates reflux symptoms. Complications of esophageal dysmotility include esophagitis, esophageal strictures, Barrett's oesophagus, and bleeding. Gastric involvement may manifest as delayed gastric emptying (gastroparesis), resulting in early satiety, bloating, nausea, vomiting, and anorexia, potentially leading to malnutrition and weight loss[7,8]. In this case, the chief complaint was epigastric pain associated with frequent nausea, belching, and early satiety, for which she underwent endoscopy on multiple occasions with inconclusive findings, adding further support to the above statement.

Different studies led by different scholars over a period of time have shown different outcomes, demonstrating the utmost need and importance of prompt recognition and early intervention to halt disease progression, necessitating the need for an autoantibody test at the earliest possible time. Alongside this, a comprehensive study led by Bobeica *et al*.[4] noted that, although calcinosis seems to be less common in SSc, its association with other clinical features is characteristic of CREST syndrome and is the key element of CREST syndrome, but in this case, there was no evidence of calcinosis on comprehensive clinical evaluation and there were no structural abnormalities or signs of pulmonary artery hypertension (PAH) in echocardiography (Echo), which in turn emphasises, the need for further studies that may contribute to a reassessment regarding the presence of calcinosis in CREST syndrome as a key element, since it may not always present along with other clinical findings in CREST syndrome. Patients require regular clinical follow-up with early pulmonary function tests and echocardiography to assess the clinical course of the disease and related complications because CREST syndrome coupled with pulmonary hypertension (elevated blood pressure within the lungs) can lead to heart and respiratory failure. Here, Table 4 demonstrates the overview of CREST syndrome.

Table 4

Overview of CREST syndrome.

Incidence	About 49 cases reported up to 2024 in PubMed
Age of onset	Adult
Sex predilection	F/M sex ratio around 4.6:1[9]
Aetiology	Multigenic/multifactorial
Association/ complication	Pulmonary hypertension
Investigation	Serology (anti-centromere antibody)
Management	Mostly symptomatic (conservative) Immunosuppressive agents Physical rehabilitation
Recurrence	Rare
Prognosis	Relatively good with long-lasting disease duration (10-year survival rate is about 80–90%) Severe prognosis (who develop pulmonary artery hypertension as a complication of the disease, in about 10% of cases)

Conclusion

Therefore, a *conclusion* can be drawn from that although CREST syndrome is a rare clinical entity, it warrants consideration by primary physicians during evaluation. Despite its rarity, inclusion in differentials is essential to prevent the worsening of the condition and to prevent further complications. Heightened awareness among healthcare providers is pivotal for prompt recognition and appropriate management. This case also adds valuable insights to the rare cases of CREST syndrome, underlining the necessity to advocate further research into this autoimmune connective tissue disorder.

Ethical approval

Not applicable because this was a single case report obtained during routine clinical evaluation. The authors confirm that no harm was caused to the subject and that the study procedures were in compliance with the ethical standards and regulations set by the World Medical Association's Helsinki Declaration 2013.

Consent

Written informed consent was obtained from the patient for publication of this case report while being anonymous. A copy of the written consent form is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

P.G.: conceptualization, data curation, formal analysis, methodology, validation, visualisation, writing – original draft, and writing – review and editing; P.A.: conceptualization, formal analysis, validation, visualisation, writing – original draft, and writing – review and editing; D.S.: conceptualization, visualisation, and writing – review and editing; S.J.T.: writing – original

draft and writing – review and editing; M.T.: data curation, investigation, methodology, writing – original draft and writing – review and editing. For important intellectual content, all authors approved the final manuscript.

Conflicts of interest disclosure

All authors declare that there are no conflicts of interest regarding the publication of this paper.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Pukar Gupta, Pradeep Adhikari, and Muktinath Thapa.

Data availability statement

The data and material used in this case report are available upon request from the corresponding author.

Provenance and peer review

Not applicable.

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