CASE REPORT

CREST syndrome: a patient with very early diagnosis of systemic sclerosis

Síndrome CREST: paciente con diagnóstico muy temprano de esclerosis sistémica

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ABSTRACT

Background: Systemic sclerosis is a rare autoimmune disease that can rapidly progress to organ involvement. Very early diagnosis (VEDOSS) may allow timely intervention, yet some patients still develop severe complications. **Case presentation:** A 42-year-old woman presented with a 3-year history of arthritis, Raynaud's phenomenon, skin thickening, dysphagia, weight loss, dyspnea, and digital ulcers. Exams revealed telangiectasias, sclerodactyly, calcinosis, restrictive spirometry, ILD on HRCT, and positive anti–Scl-70 antibodies. She initially received mycophenolate mofetil without improvement, followed by rituximab with clinical stabilization. **Conclusions:** This very early yet rapidly progressive systemic sclerosis case underscores the need for prompt recognition and individualized therapy, as organ damage may occur despite early management.

Keywords: Systemic Sclerosis (SSc); Interstitial Lung Disease (ILD); Very Early Diagnosis of Systemic Sclerosis (VEDOSS)

RESUMEN

Introducción: La esclerosis sistémica es una enfermedad autoinmune poco frecuente que puede progresar rápidamente hacia la afectación de órganos. El diagnóstico muy temprano (VEDOSS) permite intervenir oportunamente, aunque algunos pacientes desarrollan complicaciones graves. **Presentación del caso:** Paciente femenina de 42 años, con tres años de artralgias, fenómeno de Raynaud, engrosamiento cutáneo, disfagia, pérdida de peso, disnea y úlceras digitales. Los estudios revelaron telangiectasias, esclerodactilia, calcinosis, patrón restrictivo en espirometría, EPI en TACAR y anticuerpos anti–Scl-70 positivos. Fue tratada inicialmente con micofenolato sin mejoría, seguido de rituximab, con estabilización clínica. **Conclusiones:** Este caso de diagnóstico muy temprano pero de progresión rápida resalta la importancia del reconocimiento oportuno y del tratamiento individualizado, ya que el daño orgánico puede ocurrir pese al manejo precoz.

Palabras clave: Esclerosis sistémica; Enfermedad pulmonar intesticial; Diagnóstico muy temprano de esclerosis sistémica

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease (CTD) that is associated with substantial morbidity and mortality due to fibrosis and vasculopathy, as well as cellular and humoral immune response abnormalities; the estimated prevalence is 30–120 cases per million.[1] To date, systemic sclerosis is considered an orphan disease, with no validated strategy of Disease-Modifying Antirheumatic Drugs (DMARD) treatment for all patients.[1-3]

The disease spectrum ranges from limited cutaneous forms, such as CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasias), to diffuse cutaneous involvement with rapid progression and early internal organ damage. Identifying patients in the very early stages of systemic sclerosis (VEDOSS) is crucial, as it may allow for interventions aimed at preventing or slowing the progression of irreversible organ complications, particularly interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH).

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CASE PRESENTATION

A 42-year-old woman presented to the outpatient rheumatology clinic with a 3-year history of inflammatory arthralgias affecting the small joints of the hands, feet, and shoulders. She rated the pain intensity as 10 out of 10 on a numerical rating scale, with maximal severity during the morning hours, partial relief with physical activity, and transient response to non-steroidal anti-inflammatory drugs (NSAIDs). Associated symptoms included alopecia and noticeable changes in skin texture and turgor on the upper extremities.

Two years prior to presentation, she began experiencing Raynaud's phenomenon, characterized by triphasic color changes (pallor followed by cyanosis and erythema) in her fingertips, triggered by cold exposure and minor trauma. Approximately 18 months later, she developed progressive skin thickening involving the fingers, lower extremities, and trunk.

Over the preceding three years, the patient reported unintentional weight loss of approximately 8.6 kg (19 lbs), accompanied by dysphagia for solid foods, anorexia, and significant asthenia. She also described the onset of a persistent non-productive cough, exertional dyspnea, and sporadic subjective fever.

Multiple prior medical consultations for these symptoms resulted in treatments with various antibiotics (amoxicillin/clavulanic acid, levofloxacin, cefixime) and NSAIDs, which provided no symptomatic relief. Her cough persisted and worsened, becoming refractory to antitussive medications. Functional capacity declined significantly, with reduced tolerance for ambulation and debilitating chronic fatigue. Four months before the current evaluation, the patient experienced an episode of hematemesis, requiring emergency department admission. An upper endoscopy at that time revealed esophagitis with superficial mucosal tears. No additional recent laboratory results were available for review.

Her personal and family medical history was non-contributory. On physical examination, she was afebrile, with a blood pressure of 125/75 mmHg, heart rate of 98 bpm, respiratory rate of 22 breaths per minute, and oxygen saturation of 92% on room air. Her body mass index was 24.3 kg/m^2. A 6-minute walk test demonstrated desaturation from 92% to 87%, with a walked distance of 82 meters. A pulmonology evaluation and subsequent pulmonary function tests revealed a restrictive pattern on spirometry. Cutaneous examination revealed microstomia, facial and chest telangiectasias (Figure 1A and

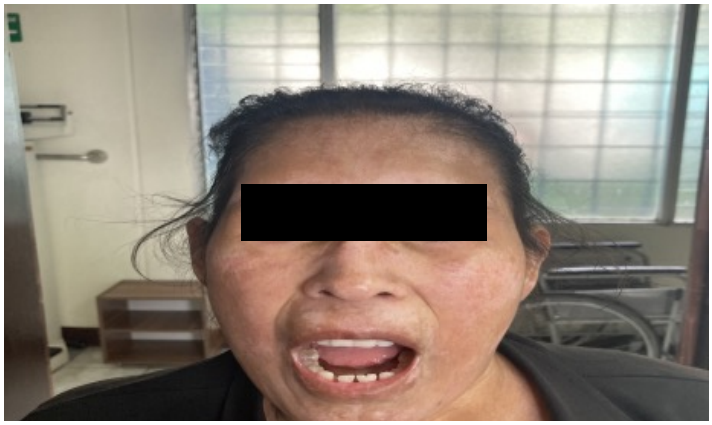

Figure 1A. Photograph of the face showing microstomia.

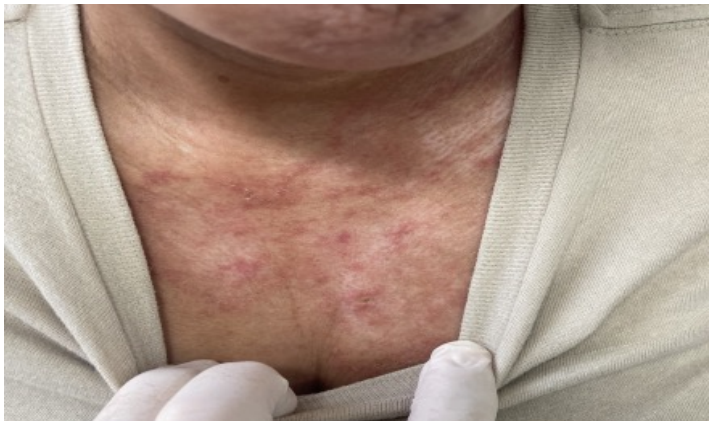

Figure 1B. Photograph of the chest showing telangiectasia.

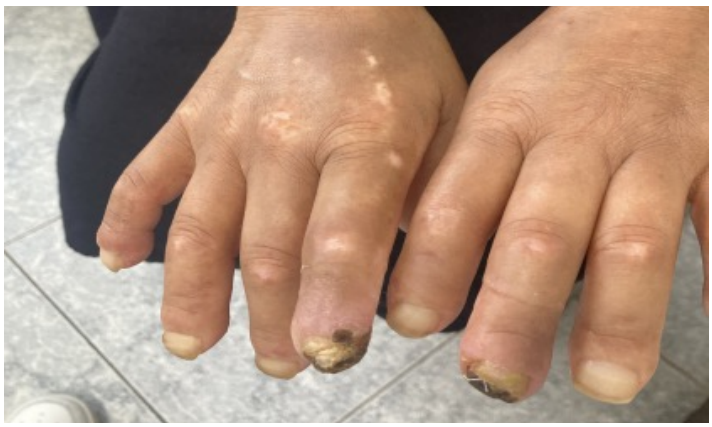

Figure 2A

Figure 2B

Figure 2 A and B. Photograph of the hands showing ulcers on second right finger and third left finger, calcinosis on fingertips, sclerodactyly and skin thickening on hands and fingers with modified rodnan score of 10 points.

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1B), and thickened skin consistent with scleroderma on the chest, upper and lower extremities. Mucous membranes were dry. Pulmonary auscultation revealed fine crackles at the right lung base. Digital examination showed signs of Raynaud's phenomenon (rubor phase), active digital ulcers on the second right and third left fingertips, calcinosis cutis, and sclerodactyly (Figure 2).

One of the first signs of complication is the Raynaud's phenomenon, supposedly preceding other symptoms of systemic sclerosis by 2 to 5 years. Nailfold videocapillaroscopy (NVC) of the fingers showed mega capillaries (Figure 3).

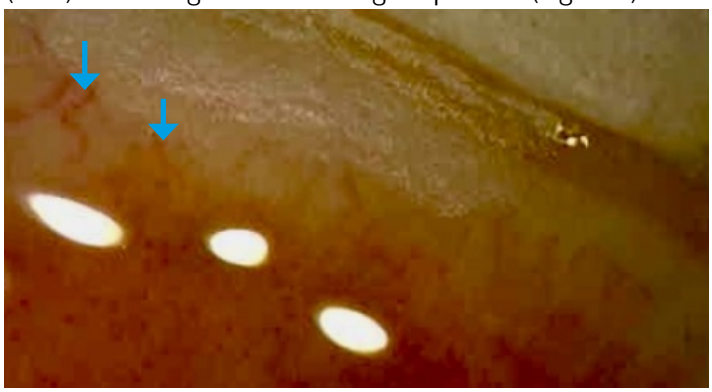

Figure 3. Photograph of NVC (magnified 200X). Blue arrows showing turtuous megacapillaries.

Laboratory and Imaging

Initial laboratory studies showed mild anemia, elevated inflammatory markers (HS-CRP 4.01 mg/L; ESR 53 mm/hr), severe vitamin D deficiency, and a strongly positive anti–Scl-70 antibody (>200 U/mL), consistent with active systemic sclerosis. ANA was positive with a homogeneous pattern at 1:160. Renal and liver function were within normal limits. (Table 1). Follow-up tests during treatment showed fluctuations in CRP and ESR, with improvement after rituximab. High-resolution chest CT demonstrated pleural nodular thickening, fine subpleural and interstitial reticulations, ground-glass areas, mild bronchiectasis, and small nodules across both lung fields, confirming interstitial lung disease compatible with SSc. (Figure 4).

Table 1. Laboratory results

Variable	Reference Range	Upon consultation	Control laboratory results (with MMF)	Control laboratory results (with RTX)
Hemoglobin (g/dl)	11.5-17.5	11.2		11.7
Hematocrit (%)	35-50	34.2		35.9
White blood cell (per-µl)	3.5-9.5	6.35		7.8
Differential count (per-µl) Neutrophils Lymphocytes Eosinophils	 50-70 20-50 0.4-8.0	 66.4 24.5 0.6		 68.2 22.1 0.9
Platelets (per-µl)	125-450	346		421
HS CRP (mg/l)	<1: low risk 1-3: intermediate risk >3: High risk	4.01	7.39	3.4
ESR (mm/hr)	0-20	53	92	45
SGOT/SGPT (U/l)	1-39/1-42	22.5/16.58	81.32/46.07	19.72/13.44
Cr/ Bun (mg/dl)	0.5-1.3/6-24	0.79/ 9.46		
25-OH vitamin D3/D2 (ng/ml)	≥30<150	16.5	22.04	32.6
Anti Scl 70 (U/ml)	<15	>200		
RF (U/ml)	<8	<8		
Anti CCP (U/ml)	<20	12		
ANA	Negative/ dilution < 1:80	Homogenous 1:160		
Urine test	Negative	Negative		

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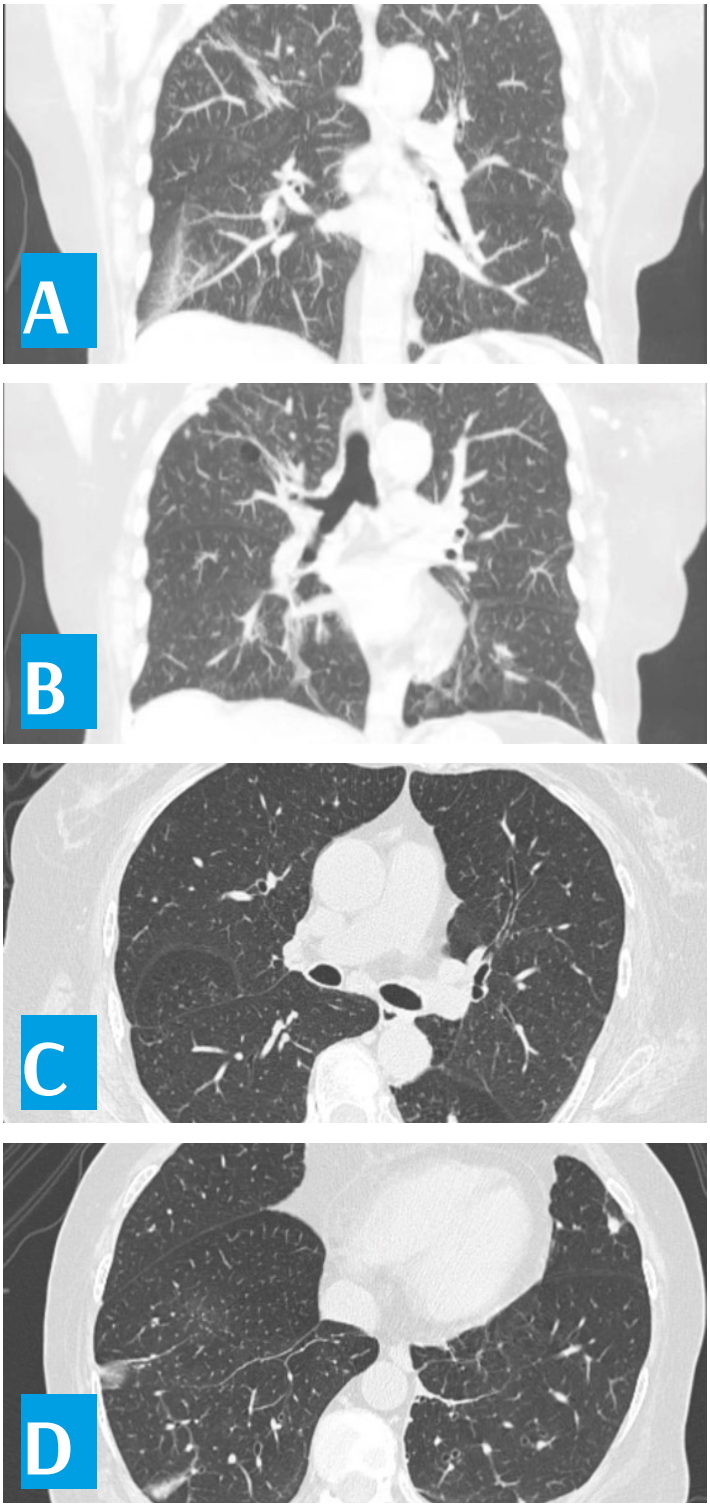

Figure 4. High Resolution Chest CT scan.
Description: Figures A and B show nodular pleural thickening of the right upper lobe with fine irregular subpleural and interstitial reticular changes, small nodules in both lung fields, mild bronchiectasis with a small bullae in the right upper lobe, and subsegmental atelectasis in the bases of the lungs. Figure C shows fine subpleural and interstitial reticular changes in the lower segments, thin ground-glass areas, small nodules in both lung fields and mild bronchiectasis. Figure D shows nodular pleural thickening of the right upper lobe with fine subpleural reticular changes.

Diagnosis and management

Diagnosis:

1. CREST syndrome: Diffused Cutaneous Systemic Sclerosis (DCSSc).
2. Interstitial Lung Disease (ILD).

The American College of Rheumatology and European Alliance of Association for Rheumatology Classification Criteria for Systemic Sclerosis (2013):

Skin thickening of fingers and both hands: 9 points
Raynaud's phenomenon: 3 points
Anti Scl 70 (+): 3 points
Telangiectasia: 2 points
Fingertip lesions: 2 points
Digital tip ulcers: 2 points

Total: 21 points; 9 points are required to establish the diagnosis.

Management:

Initially, the patient was treated with mycophenolate mofetil (MMF) 500mg PO BID, then increased every two weeks by 500mg daily until a maximum dose of 1.5gr BID was reached. After 2 months of no improvement, Rituximab (RTX) was administered at a dose of 500mg IV STAT and every 6 months.
Additional treatment included:
Irbesartan 150mg PO QD (nephro protector)
Sildenafil 20mg PO QD
Atorvastatin 10mg PO QD
Etoricoxib 90mg PO QD PRN
Nifedipine 20mg PO BID
Esomeprazole 40mg PO QD
Vitamin D3 (100,000IU) PO monthly
These additional medications are often used as a prophylaxis measure. Due to its extensive systemic damage, certain medications like sildenafil are used in pulmonary hypertension, nifedipine in Raynaud's phenomenon, esomeprazole in acute or chronic gastritis, and vitamin D3, which exerts pleiotropic actions. Patient reported improvement with all these medications.

DISCUSSION

This case illustrates a patient meeting criteria for VEDOSS who subsequently developed a rapidly progressive form of CREST syndrome, culminating in significant organ damage, notably ILD and esophageal dysmotility. These complications represent major causes of morbidity and mortality in SSc.[4]

SSc encompasses a spectrum of disease, with the diffuse cutaneous subtype characterized by rapid progression of skin induration and early internal organ involvement, portending a poor prognosis marked by frequent disability and high mortality.[3,5] Currently, no curative disease-modifying antirheumatic therapy exists. Our patient failed to demonstrate clinical improvement with mycophenolate

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mofetil (MMF) but achieved significant stabilization following rituximab (RTX) initiation.

This differential treatment response highlights the therapeutic challenge in SSc. While a systematic review and meta-analysis supports the efficacy of MMF for improving skin fibrosis,[6] another meta-analysis suggests that RTX is associated with stabilization of lung function.[7] Reflecting this evidence, the American Thoracic Society conditionally recommends RTX for SSc-ILD, while strongly recommending MMF.[8] Our patient's lack of response to MMF underscores the need for personalized treatment approaches.

Pulmonary arterial hypertension (PAH) is another severe complication of SSc, occurring in 8–12% of patients and representing a leading cause of death.[9] Inception cohort studies identify predictors of early mortality, including male sex, older age at onset, diffuse disease, PAH, scleroderma renal crisis, and anti-Scl-70 positivity.[10] Although our patient's transthoracic echocardiogram showed no signs of PAH, the gold standard for diagnosis remains right heart catheterization, which was not performed and constitutes a limitation of this report.[9]

NVC findings may reflect systemic microvascular damage. Significant capillary loss and late NVC patterns have been correlated with the presence and severity of PAH in SSc patients, suggesting a role for NVC in risk stratification.[11]

The VEDOSS concept aims to identify patients in the earliest phases of SSc, typically within 3–5 years of symptom onset, as in our patient's 3-year history.[12] Despite early recognition, significant organ damage can still develop, highlighting the aggressive nature of some disease variants. A pre-scleroderma phase, characterized by Raynaud's phenomenon and specific autoantibodies without other clinical manifestations, often precedes overt disease.[2,9-11]

Esophageal involvement is nearly universal in SSc, manifesting as impaired motility and reduced lower esophageal sphincter pressure, leading to severe reflux and potential complications such as hematemesis, as observed in this case.[13]

Furthermore, the presence of antinuclear antibodies (ANAs), particularly at high titers (>1:80), is associated with greater disease activity and severity in systemic sclerosis.[4,12]

CONCLUSION

This case of VEDOSS exemplifies a rapidly progressive disease course despite timely recognition. The patient's favorable response to rituximab, following an inadequate response to mycophenolate mofetil, highlights the critical need for individualized therapeutic strategies and close monitoring in SSc. The development of ILD and significant esophageal involvement, even within a short timeframe, underscores that organ damage can manifest early and aggressively. Current management led to symptomatic improvement, including reduced dyspnea, healing of digital ulcers, and better nutritional tolerance, with a planned initiation of nintedanib. This case reinforces that SSc remains a complex disease with a variable and often unpredictable trajectory, necessitating a multifaceted treatment approach and ongoing research to discover more effective, targeted therapies.

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- Francia Denisse Hernández Guifarro: Validation, review and edition.

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