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## CASE STUDY



# COVID-19 as a possible risk factor for poor prognosis in systemic sclerosis

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## ABSTRACT

**Introduction.** Scleroderma Renal Crisis (SRC) is a life-threatening complication of systemic sclerosis (SSc), traditionally associated with anti-RNA polymerase III antibodies, corticosteroid use, and diffuse skin involvement. However, the role of COVID-19 as a potential trigger for SRC remains poorly understood. This study explores the occurrence of COVID-19-associated SRC, focusing on its clinical presentation, underlying risk factors, and outcomes.

**Case presentation.** We present a case series of two unvaccinated patients with systemic sclerosis who developed SRC following COVID-19 infection, despite the absence of traditional risk factors. Clinical features, laboratory findings, renal histopathology, and disease progression were analyzed to assess potential mechanisms linking SARS-CoV-2 infection to SRC onset. Both patients developed abrupt-onset malignant hypertension and acute kidney injury after supporting the COVID-19. Neither patient had a history of corticosteroid use or known anti-RNA polymerase III positivity, suggesting an alternative mechanism of SRC activation. Notably, both cases had pre-existing renal anomalies (renal developmental abnormality and prior nephrectomy), which may have contributed to increased susceptibility. Despite aggressive management, both patients developed dialysis-dependent renal failure and succumbed to SRC-related complications.

**Conclusions.** Our findings highlight COVID-19 as a potential trigger for SRC, possibly through endothelial dysfunction, inflammatory cytokine storms, and renal microangiopathy. The presence of pre-existing kidney conditions may further predispose SSc patients to SRC following SARS-CoV-2 infection. Additionally, the lack of vaccination in these cases raises the question of whether COVID-19 immunization could reduce SRC risk. Further research is needed to elucidate the pathophysiology, risk stratification, and long-term outcomes of COVID-19-associated SRC, as well as the role of vaccination in prevention.

**Keywords:** COVID-19, scleroderma renal crisis, systemic sclerosis, acute kidney injury, SARS-CoV-2.

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## Key messages

### What is not yet known on the issue addressed in the submitted manuscript

Currently, the influence of COVID-19 infection on the evolution and prognosis of systemic sclerosis, as well as the role of anti-covid vaccination in preventing major complications, is unknown.

### The research hypothesis

COVID-19 infection exacerbates the progression of systemic sclerosis and serves as a potential trigger for scleroderma renal crisis, particularly in patients with pre-existing kidney conditions.

### The novelty added by the manuscript to the already published scientific literature

The manuscript contributes to the understanding of COVID-19 infection as a trigger factor for renal complications in systemic scleroderma and indicates the need to study the role of anti-covid vaccination to reduce severe complications of the disease.

## Introduction

Systemic sclerosis (SSc) is an autoimmune, multisystem connective tissue disorder marked by extensive vascular dysfunction and the gradual development of fibrosis in the skin as well as internal organs, including kidneys [1]. The most severe manifestation of renal involvement in systemic sclerosis is the scleroderma renal crisis (SRC), an infrequent complication. The reported incidence is 7-9% in individuals with diffuse SSc and 5-6% in those with the limited SSc [2]. The pathogenesis of SRC involves endothelial damage, intimal proliferation, and the constriction of kidney arteries, resulting in reduced renal blood flow. This sequence of events induces hyperplasia of the juxtaglomerular apparatus, consequently elevating renin levels leading to acute hypertension and renal dysfunction [3].

COVID-19, caused by SARS-CoV-2, has disproportionately impacted individuals with underlying autoimmune conditions due to their increased susceptibility to infection and disease exacerbation. The SARS-CoV-2 virus has shown a direct and indirect impact on kidney function through mechanisms such as viral invasion of renal cells, hyperinflammation, and vascular injury [4]. These overlapping pathophysiological pathways raise concerns about worse outcomes in SSc patients affected by COVID-19. SARS-CoV-2 targets the kidneys via angiotensin-converting enzyme 2 (ACE2) receptors, leading to direct cytotoxicity, endothelial dysfunction, and microvascular thrombosis [5]. These mechanisms overlap with the vascular pathology seen in SSc, exacerbating renal damage. The impact of COVID-19 infection on the development of kidney damage is well-documented. Common kidney biopsy findings associated with COVID-19 include acute tubular damage, collapsing glomerulopathy (a variant of focal segmental glomerulosclerosis, and thrombotic microangiopathy. Additionally, acute tubular injury is frequently observed in COVID-19 patients with acute kidney injury (AKI). Several glomerular diseases have been linked to COVID-19 infection, encompassing crescent glomerulonephritis, minimal change disease, focal segmental glomerulosclerosis, vasculitis (including anti-neutrophil cytoplasmic antibody-associated vasculitis, anti-glomerular basement membrane disease, and immunoglobulin A vasculitis with nephritis), membranous nephropathy, lupus nephritis, and acute tubular injury. Furthermore, mixed pathologic renal lesions, acute interstitial nephritis and treatment-related AKI have been reported in COVID-19 patients [6-8].

Moreover, a case report has documented the onset of systemic sclerosis subsequent to a mild COVID-19 infection in a previously healthy individual. The authors proposed that there are certain parallels between COVID-19 infection and systemic sclerosis [9]. Exposure to corticosteroids at doses exceeding 15 mg (frequent use in the treatment scheme for COVID-19 infection) per day in the preceding 6 months is a major recognized risk factor [10].

Ferri *et al.* (2021) assumed the virus might exacerbate pre-existing manifestations of systemic sclerosis during the acute phase of COVID-19 infection. However, over the long term, this interaction could potentially lead to complex organ damage [11].

## Cases presentation

### Patient no. 1

A 46-year-old female presented with symptoms indicative of SSc, beginning in May 2016. Clinical manifestations included edema affecting the hands and face, cutaneous thickening extending to the knees with associated flexion difficulties, and a concomitant esophageal burning sensation. In June 2016, the onset of Raynaud's phenomenon, characterized by pallor in the digits, further prompted clinical evaluation. Diagnostic workup revealed positive ANA and ATA antibodies, with negative anti-RNA polymerase III antibodies. Methotrexate, 10 mg/week and Amlodipine, 10 mg/day was started, this leading to an improvement in her overall condition.

In December 2019, she was diagnosed with viral hepatitis. At the same time, lung CT presented pulmonary fibrosis with multiple ground-glass opacities. She received antiviral treatment with Tenofovir 300 mg daily, and in March 2020 treatment with Cyclophosphamide therapy was initiated at 1000 mg, intravenously once a month, which was then stopped due to the pandemics.

On November 10, 2020, the patient presented symptoms indicative of an acute respiratory viral infection, and a subsequent PCR test confirmed COVID-19 infection. She was admitted to the hospital, and received treatment included antiviral, antibacterial medications, and glucocorticosteroids (Methylprednisolone up to a maximum of 12 mg/day), and symptomatic care. The patient's general condition deteriorated, with the onset of muscle weakness, diarrhea, and worsening dyspnea. On December 10, 2020, a chest CT scan revealed diffuse areas of pulmonary tissue induration with bilateral ground-glass opacities. Additionally, a *Clostridium difficile* infection was detected, leading to the initiation of antibiotic therapy. The patient continued treatment with Methylprednisolone at a reduced dosage of 8 mg/day, vasodilators, and symptomatic care.

Throughout 2021, the patient experienced progressive skin involvement characterized by thickening in the arms, forearms, chest, and thighs, accompanied by worsening respiratory function. Gastrointestinal involvement also progressed, and Raynaud's syndrome persisted. Treatment with methylprednisolone at a reduced dosage of 4 mg/day, vasodilators and proton pump inhibitors was continued.

Chest CT repeated on 09.02.2022 showed disease progression with an increase in fibrotic changes, multiple ground glass and paving stone opacities, some cylindrical bronchiectasis, dilation of the esophagus. During this period, the patient underwent immunosuppressive therapy with Cyclophosphamide 1000 mg, alongside maintenance medications including Methylprednisolone at 4 mg/day, Amlodipine at 10 mg/day, and Pantoprazole at 20 mg/day. Unfortunately, there was no discernible improvement. Subsequently, Azathioprine was recommended as an alternative, but it was discontinued after two weeks due to adverse reactions, including general weakness, dizziness, and visual disturbances. Regrettably, the patient's condition continued to deteriorate progressively.

During the patient's most recent hospitalization spanning from April 4, 2023, to April 10, 2023, a comprehensive examination was conducted, yielding the following results:

*Physical examination:* diffusely hyperpigmented skin, Rodnan score 46, telangiectasias on the face and chest, mod-

erate leg edema, bilateral harsh breath sounds on auscultation, with fine basal bilateral crackles, respiratory rate: 19 breaths/minute, SpO<sub>2</sub>: 93% on room air, Blood pressure - 180/110 mmHg, periodically increasing to 240/140 mmHg; heart rate: 82 bpm; dry, coated tongue, liver palpable +3-4 cm; Diuresis measured at 400 ml/24 hours.

*Laboratory and imaging findings:* leukocytosis, reticulocytosis, Creatinine - 451.2 - 623.7 - 540.4 - 534.2 mmol/l; Uric acid - 611.3 mmol/l; Urea - 33.02 mmol/l; Proteinuria - 10 g/l; clear urinary sediment.

*Kidney ultrasound:* asymmetrically renal positioning, left kidney displaced to the lumbar region; horseshoe kidney on the right measuring 90x40 mm; left kidney 96x40 mm, mildly deformed bilateral pelvicalyceal system.

*Treatment:* glucocorticosteroid (Methylprednisolone 4 mg/day); histamine 2 receptor antagonists (Famotidine); calcium channel blockers (Amlodipine); angiotensin converting enzyme inhibitors (Ramipril), synthetic prostaglandin analog (Alprostadil); diuretics (Torsemide).

*Disease progression:* on April 11, 2023, the patient was discharged from the hospital at her own request, and 2 days later had died at home.

## Patient no. 2

A 67-year-old female with no prior history of rheumatic pathology presented with symptoms in November 2021, including inflammatory arthralgia in the small joints of the hands bilaterally and paresthesia. The patient initially used NSAIDs and local ointments, resulting in subsequent improvement. In December 2021, she developed an acute respiratory viral infection marked by low-grade fever, sore throat, and a runny nose. Following a positive PCR test for COVID-19 infection, she received symptomatic treatment at home. After recovering from the SARS-CoV-2 infection, the patient observed the onset of edema in the hands, progressing to the forearms and the lower third of the arms. Subsequently, swelling occurred on the shins, thighs, and lower abdomen. From the patient's personal history, she underwent a left kidney nephrectomy 20 years ago due to suspected neoplasia, though the specific diagnosis was not clarified.

In May 2022, the patient sought consultation with a rheumatologist, reporting the aforementioned complaints, including arthralgia in the small joints of the hands, scapulo-humeral, hip, and knee joints, muscle weakness, xerostomia, difficulty swallowing, exertional dyspnea, and pronounced general weakness. A comprehensive evaluation revealed the following: ANA (Antinuclear Antibody): 1/5120; Anti-Scl70 - positive; anti-RNA polymerase III antibodies - negative. The diagnosis of active diffuse systemic sclerosis (EUSTAR score = 5 points) was established. Treatment was initiated with Methylprednisolone 4 mg/day, Azathioprine 100 mg/day, and Nifedipine 10 mg/day. However, the patient demonstrated poor compliance with the prescribed treatment.

Over time, the patient's symptoms, including arthralgia, myalgia, general weakness, and generalized peripheral edema, along with uncontrolled hypertension, escalated. Consequently, she was admitted to hospital from September 20, 2022, to October 4, 2022, with suspected scleroderma renal crisis. Objective findings during the examination included scleroderma manifestations such as indurated skin on the hands, forearms,

arms, thighs, and legs (Rodnan score 38), with hands exhibiting flexion contractures and digital ulcers. Telangiectasias were observed on the face, chest, and flanks, along with microstomia. Auscultation revealed harsh breath sounds, subcrepitant and crepitant rales at the base. Blood pressure measuring 200/96 mmHg, and a heart rate of 80 bpm were noted. The patient reported frequent urination and nocturia.

Blood tests indicated the following deviations: leukocytosis and anemia, azotemia (creatinine 1017 mmol/l, urea 56 mmol/l, hyperkalemia - 7.02 mmol/l). Bacteriological examination of urine indicated hemolytic *E. coli* with a titer of 10<sup>7</sup>. Blood bacteriological examination was sterile. Esophagus radioscopy revealed mucosal smoothing and reduced peristalsis, and a chest X-ray disclosed bilateral pleurisy with pleural effusion from ribs 5 to the diaphragm.

The patient underwent an evaluation by a nephrologist, leading to the diagnosis of Scleroderma renal crisis and chronic kidney disease. Hemodialysis sessions were initiated, but the patient poorly tolerated the procedure, experiencing apathy and mild confusion.

The patient was transferred to the intensive care unit due to a worsening general condition, leading to cardiogenic obstructive shock, severe left ventricular outflow tract obstruction and respiratory failure. Pneumonia by stasis and bilateral pleurisy were noted.

Despite antibiotic therapy, antihypertensives (including angiotensin converting enzyme inhibitors, calcium channel blockers, and diuretics), and anticoagulants, the patient's condition deteriorated. On the fourth day of hospitalization, the patient became anuric despite adequate intravenous fluid hydration and diuretic therapy, and edema progressed to anasarca. Hemodialysis sessions were initiated, resulting in a positive trend in urea and creatinine levels. Although the patient remained hemodynamically stable without vasopressor support, respiratory failure ensued, necessitating O<sub>2</sub> therapy at 6 l/min via a simple face mask. By the tenth day, assisted ventilation became necessary. A chest X-ray revealed alveolar pulmonary edema in subtotal bilateral pleuropneumonia, alongside bilateral pleurisy. A diagnosis of uro-nephrogenic, pulmonary septic shock was established, with subsequent progression to septic MODS and end-stage renal disease. The disease trajectory turned negative due to toxicoseptic shock, febrile syndrome, and significant leukocytosis. On the fifteenth day of hospitalization, the patient experienced cardiac arrest due to asystole, occurring in the context of mechanical ventilation and high doses of catecholamines.

## Discussions

Scleroderma renal crisis (SRC) is a rare but potentially devastating complication of systemic sclerosis as it is associated with significant morbidity and mortality.

SRC classically develops in patients with early or progressive diffuse cutaneous disease or positivity for anti-RNA polymerase III antibodies. Other risk factors for SRC are pericardial effusion, tendon friction rub and steroid use. COVID-19 has been reported to cause TMA by inducing immune dysregulation via an overactive complement system. It is plausible that infection with COVID-19 triggered an exaggerated immune response, in turn leading to the development of SRC

in our patient. COVID-19 may trigger SRC in patients with systemic sclerosis in the absence of other risk factors.

Salman Mahmood *et al.* have presented case of a 37-year-old female patient who did not have any such risk factors and rather developed SRC following infection with COVID-19 leading to dialysis dependence [7]. Described patients were also negative for anti-RNA polymerase III antibodies, but still suffered from the diffuse form of the disease and one of them was in the early phase of the disease.

Doron Rimar *et al.* have reported a case of scleroderma renal crisis (SRC), following COVID-19 infection, in a limited-SSc patient who was in long remission prior to the infection without any risk factors for SRC [6]. The temporal relationship and lack of other risk factors combine to suggest COVID-19 infection as a possible trigger for SRC. Authors have discussed the shared pathophysiology of COVID-19 infection and SRC, including, vasculopathy, endothelial activation, hypercoagulability, cytokines release as interleukin 6, that may explain the possible role of COVID-19 infection, as a trigger for SRC in SSc patients.

Despite the fact that our patients have not been vaccinated against COVID-19, there are reported cases of kidney injury following vaccination for coronavirus disease 2019 (COVID-19) with a focus on renal pathology. One review published in 2022 have found 49 case reports [12]. These included minimal change disease (n = 17), IgA nephropathy (IgAN) (n = 15), IgA nephritis/vasculitis (n = 5), ANCA glomerulonephritis/vasculitis (n = 5), anti-glomerular basement membrane (GBM) nephritis (n = 2), and 1 case of each granulomatous vasculitis, acute tubulointerstitial nephritis, scleroderma renal crisis, IgG4-related disease nephritis, and primary membranous nephropathy (MN). Further investigations of the underlying pathogenesis of post-COVID-19 vaccination renal adverse events are required.

Exposure to corticosteroids can trigger scleroderma renal crisis. A case was reported involving a female patient who developed systemic sclerosis post-COVID-19 infection. Following exposure to corticosteroids, the patient developed scleroderma renal crisis complicated by thrombotic microangiopathy, seizures and acute renal failure. Despite an antibody profile not typically associated with renal crisis (anti-topoisomerase positive, anti-RNA- polymerase III negative), the patient developed recurrent renal crisis with repeated exposure to corticosteroid therapy, highlighting the risk of steroid use in all patients with systemic sclerosis [10]. Our patients were treated with glucocorticosteroids, but in low doses, which may not be considered a risk factor for the development of SRC.

A common feature in both presented cases were the pre-existing kidney diseases (in the first patient - congenital anomaly of the kidneys and in the second - unilateral nephrectomy) which can also be considered risk factors for SRC in patients who have suffered from COVID-19.

## Conclusions

In both of the presented cases, COVID-19 infection worsened the progression of systemic sclerosis and ultimately led to the death of the patients through the development of scleroderma renal crisis. Of all the known risk factors for scleroderma renal crisis, the described patients presented only the diffuse form of the disease. Additionally, the pres-

ence of pre-existing kidney abnormalities—congenital anomalies in the first patient and unilateral nephrectomy in the second—may also be considered potential risk factors for the development of SRC in individuals with systemic sclerosis who have experienced COVID-19 infection.

## Competing interests

None declared.

## Authors' contribution

SA, SP, ER conceptualized and designed the study. SA, SP, LR, ER, LD, IM, VS conducted patients and collected their data. SA drafted the manuscript. SP supervised the project and reviewed the manuscript. All authors read and approved the final version of the manuscript.

## Informed consent for publication

Obtained.

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