

## COVID-19 in a patient with systemic sclerosis with pulmonary fibrosis: case report

### *COVID-19 em portadora de esclerose sistêmica com fibrose pulmonar: relato de caso*

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**ABSTRACT:** This report aims to describe a case of COVID-19 in a female patient, 48 years old, with diffuse cutaneous Systemic Sclerosis (dcSSc) for 14 months associated with pulmonary fibrosis, using mycophenolate mofetil (MMF). The patient was admitted to the hospital with a one-week history of cough and fever. After 4 days, she tested positive for COVID-19. She was discharged after 11 days. Immunosuppressants are expected to predispose a greater risk of infections and consequent greater aggression to the organism. This report aimed to analyze this correlation, since the patient survived the infection and did not have a severe form of the disease. Although this report describes a patient's favorable evolution, the relevance of further studies to assess the effects of immunosuppression on COVID-19 is highlighted.

**Keywords:** Systemic sclerosis; Pulmonary fibrosis; Coronavirus infections; Immunosuppressive agents.

**RESUMO:** Este relato objetiva descrever um caso de COVID-19 em paciente do sexo feminino, 48 anos, portadora do diagnóstico de Esclerose Sistêmica forma difusa (ESd) há 14 meses, associada à fibrose pulmonar, em uso de micofenolato de mofetil (MMF). A paciente foi internada no hospital com história de tosse e febre há uma semana. Após 4 dias, testou positivo para COVID-19 e recebeu alta após 11 dias de internação. Prevê-se que os imunossupressores predisõem a um maior risco de infecções e consequente maior agressão ao organismo. Este trabalho objetivou avaliar essa relação, tendo em vista que a paciente sobreviveu à infecção por COVID-19 e não apresentou uma forma grave da doença. Embora este relato descreva evolução favorável de um paciente, ressalta-se a relevância da realização de futuros estudos para avaliar efeitos da imunossupressão na COVID-19.

**Palavras-chave:** Esclerose sistêmica; Fibrose pulmonar; Infecções por coronavírus; Imunossupressores.

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## INTRODUCTION

China notified the World Health Organization (WHO) about the occurrence of a high number of patients hospitalized due to severe pneumonia from an unknown origin in the city of Wuhan in December 2019. The following month, they identified the viral etiology similar to the coronavirus described in bats and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV 2)<sup>1</sup>. SARS can occur and develop from Coronavirus Disease 2019 (COVID-19), named by the WHO. Due to its high transmissibility, this virus has spread rapidly worldwide, leading the WHO to officially declare it as pandemic status in March 2020<sup>2</sup>.

Most people infected by COVID-19 are asymptomatic or display mild symptoms, commonly as fever, cough, sore throat, dyspnea, fatigue, and malaise. In some patients, the disease can worsen, progressing to pneumonia and SARS. It is noteworthy that about 3% of cases progress to death, mainly due to hypercytokinemia, also known as “cytokine storm,” resulting in multiple organ failure<sup>1,2</sup>.

Some factors can contribute to the aggravation of the illness, mainly associated with comorbidities like diabetes mellitus, hypertension, cardiovascular diseases, and chronic obstructive pulmonary disease. Likewise, there is a greater risk of severe disease symptoms in individuals over the age of 70<sup>3</sup>.

There has also been a significant concern with patients with systemic autoimmune diseases. Patients who undergo immunosuppressive treatments can provoke greater vulnerability by increasing the risk of infections. In contrast, a cross-sectional study in Tuscany, central Italy, involving 458 individuals with this condition, showed apparently, these patients were not at a higher risk of becoming infected with the new coronavirus when compared to the general population<sup>4</sup>. However, the South Korean study demonstrated a higher risk of virus identification for COVID-19 patients with systemic autoimmune diseases.<sup>5</sup> In addition to the controversies regarding the risk of infection and outcome in patients with systemic autoimmune diseases, there are doubts about the immune response to infection in these individuals if they were exposed to the virus again<sup>6</sup>.

Systemic Sclerosis (SS) is characterized by vascular and autoimmune phenomena, leading to cutaneous thickening and fibrosis of internal organs. It may result in pulmonary involvement in Pulmonary Arterial Hypertension (PAH) and/or Interstitial Pulmonary Disease (ILD), which occurs to some degree in 75% of patients<sup>7</sup>. There are two clinical forms of SS: diffuse cutaneous SS (SSc), characterized by rapid progression of cutaneous involvement and early visceral involvement - strongly associated with the presence of anti-topoisomerase

(anti-Scl-70)<sup>8</sup> antibody; and limited cutaneous SS (lcSS), with slowly progressive cutaneous involvement restricted to the extremities - more related to the anti-centromere antibody<sup>8</sup>. Commonly instituted treatment consists of immunosuppression, mainly cyclophosphamide (CYC) and mycophenolate mofetil (MMF)<sup>9</sup>.

There is clinical concern that patients with SS may have a worse prognosis when affected by COVID-19 infection in this context. The association between the occurrence of pulmonary diseases and immunosuppression may represent risk factors of greater severity when infected by COVID-19<sup>3</sup>. For this reason, SS patients with ILD receiving immunosuppressants may become more vulnerable to unfavorable outcomes by COVID-19<sup>2</sup>. Because of this, this article aims to describe a case report of a patient with SSd for 14 months, associated with severe ILD, who contracted COVID-19.

## CASE REPORT

This report describes the case of a patient with SSd who was admitted to the “Hospital de Clínicas” of Uberlândia Federal University (HC-UFU), whose Reverse Transcription Polymerase Chain Reaction (RT-PCR) test was positive for COVID-19. The patient met the diagnostic criteria for SS, and it was found that she did indeed have this disease<sup>8</sup>. Thus, after inclusion in the “Plataforma Brasil” and submission to the Ethics Committee on Human Research of the Uberlândia Federal University, with consubstantiated opinion number 4,530,224, and the collection of the Informed Consent Form, the information from the electronic medical record was used for the description of this case report.

A 48-year-old female patient with SSd, associated with severe ILD (Figure 1), dyspnea on small efforts, and home oxygen therapy 2.5L/min. She was diagnosed with SS in December 2018 as she presented the following criteria according to the ACR and EULAR:

- Cutaneous thickening of the fingers on both hands, with proximal extension to the metacarpophalangeal joints;
- Ulcers on the fingertips;
- ILD;
- Raynaud’s Phenomenon is associated with an abnormal unguis capillary pattern consistent with SS;
- Presence of anti-Scl-708 antibody.

The patient was prescribed monthly intravenous (IV) doses of CYC for 11 months due to severe ILD and skin fibrosis; the last pulse was given in November 2019. After this date, she started MMF for 6 months, sildenafil and bosentan, approximately 90 days before COVID-19 infection. She had been evaluated for stem cell transplantation, but due to a Forced Vital Capacity on spirometry of less than 50%, she could not undergo this

procedure. The spirometry values before COVID-19 were as follows: pre-bronchodilator use: FVC: 39%; FEV1/FVC: 101%; and FEV1: 40%; and after bronchodilator use: FVC: 47%; FEV1/FVC: 83%; and FEV1: 39%. Carbon monoxide diffusion and the 6-minute walk test were not performed.

She developed pulmonary hypertension while the disease developed, proven after right heart catheterization, classified as group I PAH (Mean Pulmonary Artery Pressure (mPAP) > 20 mmHg, Pulmonary Capillary Pressure (PCP) < 15mmHg and Pulmonary Vascular Resistance (PVR) ≥ 3.0 Woods).<sup>10</sup>

Therefore, she was waiting for lung transplantation evaluation at the beginning of the COVID-19 pandemic.

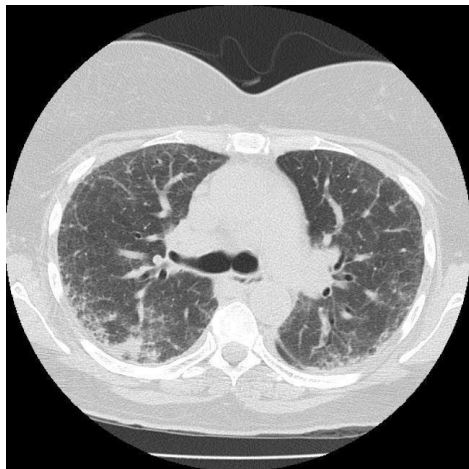


Image Description: Bilateral diffuse pulmonary involvement characterized by subpleural reticulation, ground-glass attenuation, interlobular and intralobular septal thickening, and some traction bronchiectasis. Presence of esophageal ectasia

**Figure 1:** Chest Computed tomography (CT) scan on February 3, 2020

She presented a dry cough with fever peaks measured at approximately 37.5°C on May 29, 2020. After guidance from the lead rheumatologist, treatment with levofloxacin, azithromycin, and oseltamivir was initiated on June 2, 2020, with a slight improvement of symptoms.

On June 5, 2020, she again presented a febrile peak (38.7°C), associated with worsening cough and habitual dyspnea pattern, in addition to myalgia and headache. She took dipyrone, but there was no clinical improvement. She was evaluated by the Home Care Service team, which referred her to HC-UFU. The patient was in a stable general state on admission, tachypneic, tachycardic, 96-100% saturation with O<sub>2</sub> at 2.5L/min. She denied contact with suspected or confirmed COVID-19 individuals.

On admission she reported she was taking: Mycophenolate (2g/day), Quetiapine (100mg/day), Domperidone (100mg every 8 hours), Metoclopramide hydrochloride (10mg/2ml AMP), Omeprazole (40mg/day), Nifedipine (20mg tab every 8 hours), Prednisone (5mg tab

every 12 hours), Amitriptyline hydrochloride (25mg tab./day), Diazepam (10mg tab), Amlodipine (5mg tab every 12 hours), Lactulose (667mg/L every 12 hours), Fluoxetine hydrochloride (20mg tab/day), Furosemide (20mg/2ml AMP), Prednisone (5mg tab every 12 hours), Macrogol 3350 (13.125g + 0.1 sodium bicarbonate), Levothyroxine sodium (25mcg tab/day), Micronized salbutamol spray (vial with 200 doses), Terbutaline sulfate (0.5mg/1ml AP), Enoxaparin sodium (40mg/0.4ml SUBQ), Tramadol hydrochloride (50mg cap.), Calcium Carbonate.

The patient was admitted and reported as suspected SARS, and tests were collected to analyze the presence of COVID-19. Levofloxacin and azithromycin were discontinued, and antibiotic therapy was started with oxacillin and cefepime. According to the local protocol for COVID-19 care, the use of oseltamivir was maintained to complete the recommended time taking this medication. Additionally, dipyrone was administered IV. Laboratory tests and chest CT were performed to evaluate pulmonary involvement (Figure 2) when the patient was admitted.

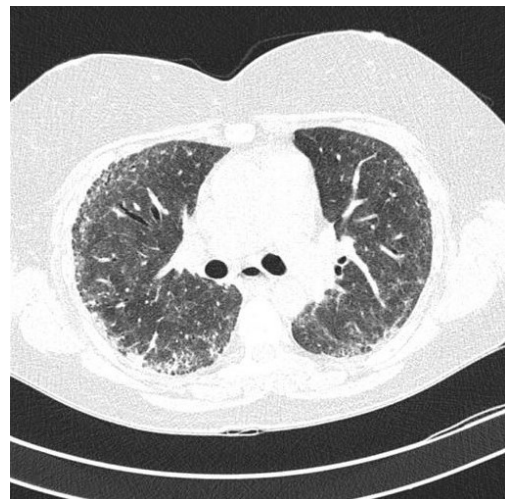


Image Description: Bilateral diffuse pulmonary involvement characterized by subpleural reticulation, interlobular, and intralobular septal thickening, some traction bronchiectasis, and discrete bilateral and sparse peripheral ground-glass opacifications. Esophageal ectasia with fluid level. Tomographic appearance compatible with interstitial pneumopathy. The possibility of scleroderma should be considered, with overlapping findings suggestive of pneumonia of viral etiology.

**Figure 2:** Chest CT dated 06/05/2020

On June 9, 2020, the patient progressed to a definite worsening of cough and saturation of 93% with O<sub>2</sub> at 1L/min, despite improving the general condition. The next day, the RT-PCR test was positive for COVID-19. Thus, the use of cefepime and oxacillin was discontinued on June 11, 2020.

After progressive improvement of symptoms and complementary test results, the patient was discharged from the hospital on June 16, 2020. She was clinically stable and undergoing the necessary evaluations to submit to the

lung transplantation when writing this article. The patient returned to HC-UFU in 2021 due to a new suspicion of COVID-19 infection, which was not confirmed.

## DISCUSSION

Despite significant advances related to the study of COVID-19, information on various aspects of the infection is still scarce regarding clinical manifestations and the treatment and prognosis, especially in less frequent epidemiological conditions, generating concern about patient follow-up by health care teams<sup>11</sup>.

For that reason, this viral infection in a patient with a history of severe SS resulted in greater apprehension from the medical team regarding prognosis. There is clinical evidence that the use of immunosuppressants predisposes to a higher risk of infections, with a strong association with cytomegalovirus, just like with other infectious agents<sup>12</sup>. Consequently, there is greater aggression to the body due to the difficulty in ensuring an effective immune defense, especially against COVID-19<sup>13</sup>. However, despite presenting SS with ILD associated with PAH and awaiting lung transplantation due to the severity of the pulmonary involvement, the patient survived the COVID-19 infection and did not require mechanical ventilation.

The questions about what determines excellent or poor evolution against COVID-19 in systemic autoimmune disease situations remain open. Probably multiple factors must be taken into account: the disease itself, the time of evolution, gender, age, the presence of comorbidities, and the drugs used. As for SS, genetic polymorphism does not clearly explain its beginning and development in multiple populations<sup>14</sup>. However, current paradigms point to immune dysregulation as a central process in the pathogenesis of SS<sup>15</sup>. There are changes in circulating cytokine levels, including IL-6, tumor necrosis factor (TNF $\alpha$ ), IL-10, and IL-4, influenced by gender, age, disease duration, and the presence of specific autoantibodies associated with SS. These laboratory changes highlight the complex immunopathogenesis of SS and point to several potential targets that can be considered for monitoring disease progression and treatment of SS<sup>15</sup>.

Cytokines and chemokines play a crucial role in the immune response against viral infections, and their altered production has been demonstrated in SARS and Middle East Respiratory Syndrome (MERS)<sup>16</sup> infections, making the COVID-19 pandemic a challenge in the management of rheumatic diseases, especially SS, which is itself a heterogeneous and complex condition. COVID-19 infection has also become a challenge in maintaining and proposing already scarce therapeutic lines for SS, with several doubts on how to manage the underlying disease and on the behavior of the drugs used in everyday inflammatory conditions<sup>16</sup>. One example is the benefit of Tocilizumab, anti-interleukin-6, in windows of

opportunity in the severe pulmonary inflammatory response of COVID-19<sup>17</sup>. Coincidentally, this drug is indicated for ILD phases of SS.<sup>18</sup> The role of MMF in modulating the viral inflammatory response is controversial since it is a pharmacological strategy frequently used in the setting of interstitial pneumopathy in SS<sup>13</sup>.

There was great concern the patient could develop into a severe form of COVID-19, characterized by an acute systemic inflammatory response resulting from cytokine storm, which could trigger multiple organ failure. This cytokine dysregulation relates to reduced production of antiviral cytokines, such as interferons (IFN), increased levels of other pro-inflammatory cytokines and chemokines, mainly the interleukins IL-1 and IL-6 and TNF $\alpha$ <sup>19</sup>.

As a result, there is excessive infiltration of inflammatory cells (such as neutrophils and monocytes) into the lung tissue, causing injury. The low production of IFN comes with the accumulation of mononuclear macrophages, which produce chemokines that attract monocytes, accentuating the presence of these elements. In addition, these produce high levels of pro-inflammatory cytokines, intensifying the cytokine storm and, consequently, the severity of the disease<sup>19</sup>.

Considering that interleukins are a group of cytokines that induce leukocyte growth and differentiation<sup>20</sup>, the increase in their production may be related to T cell hyperactivation, as seen in some patients with a severe and lethal form of the new coronavirus<sup>2</sup>. This overactivation manifests itself mainly with an increase in Th17 lymphocytes, in addition to the elevated cytotoxicity of CD8<sup>2</sup>.

The whole picture may have partially occurred in this patient, who has severe systemic involvement and reduced life expectancy due to complications, but the evolution was benign. Could the drugs be implicated in this response, associated with an individual response profile not yet well understood?

It is worth mentioning that both CYC and MMF have a regulatory role in T cell proliferation, maturation, and survival. In addition, MMF inhibits the production of IL-6 by B<sup>21</sup> cells and IL-17, with consequent specific inhibition of Th17<sup>2</sup> cells. Although SS patients are more susceptible to infection and the worsening of the condition generated by the new coronavirus, the doubt remains whether the anti-inflammatory effects of the immunosuppressants used by the patient could be implicated in the relief of severe manifestations of the disease<sup>2</sup>.

Despite the scarcity of similar case reports in the literature, a study in Italy of 916 patients with autoimmune rheumatic diseases presented a case of a patient with SS affected by COVID-19. A 54-year-old female on MMF was admitted with a history of fever, cough, and fatigue for one week. She was treated with hydroxychloroquine, azithromycin, and low oxygen flow (2L/min) and was discharged after 9 days of hospitalization<sup>22</sup>.

In another similar case report, a 57-year-old patient with SS, associated with ILD, cough, and dyspnea on exertion, taking Tocilizumab (immunosuppressant that also inhibits IL-6), developed COVID-19. They also highlighted her comorbidities: diabetes mellitus and grade 1 obesity. She sought medical attention with the symptoms of cough, headache, and malaise for one week. On admission, she was in good general condition; sub febrile (37.6°C), without significant dyspnea. Due to the mild condition, she was oriented to perform symptomatic treatment at home, with the postponement of tocilizumab infusion. During this period, she presented only mild symptoms, which ceased after 10 days<sup>23</sup>.

These reports question what factors caused benign evolution in these individuals. Would the disease itself be responsible for a protective profile, or is there a possible relationship between the use of immunosuppressants and

a specific “protection” against clinical worsening of the new coronavirus disease? Therefore, this report describes clinical and laboratory manifestations in a patient with SSd with pulmonary and cutaneous involvement, using immunosuppressive therapy, affected by COVID-19 and SARS, with worsening pulmonary involvement, but with a favorable outcome.

Although there are limitations in analyzing a single case, the evidence on the relevance of this report in a pandemic context requires urgent studies to understand the COVID-19 pathophysiology on people with severe rheumatic diseases. Finally, it is worth noting there is a need for new studies to analyze such hypotheses and seek to describe the relationship of COVID-19 to autoimmune diseases, especially SS, to provide patients with the best therapeutic options.

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**Contribution from each author:** *Ana Clara Naves Vieira and Isabela Souza Cruvinel Borges*, the authors, are both medical students at the Medical School of the Federal University of Uberlândia (UFU), contributed equally and actively in the collection, analysis, and interpretation of data related to the report, in the writing of the text, and the standardization of the norms according to the journal. The author *Juliana Markus*, professor and supervisor of the students, oriented and critically reviewed the article besides collaborating with all these steps.

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