CASE REPORT

Potential Impacts of Covid-19 on Autoimmune Diseases: A Case Report on Systemic Sclerosis

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ABSTRACT

Systemic sclerosis (SSc) is a rare autoimmune disease characterised by fibrosis of the skin, musculoskeletal system and internal organs, with clinical presentations ranging from rapidly progressive to chronic forms. The Covid-19 pandemic has highlighted potential links between infections and autoimmune diseases. We report a 49-year-old female with a history of Covid-19 reinfection who presented with long Covid symptoms. She was discovered to have a five-year history of multiple joint pain and recently developed bilateral swollen fingers with distal skin thickening extending to the elbows. Investigations revealed strong ANA and anti-Scl-70 positivity while CT thorax showed features of autoimmune interstitial lung disease. She was diagnosed to have long Covid with limited cutaneous SSc. Although the link between Covid-19 and SSc remains unclear, this case underscores the potential impacts of Covid-19 on pre-existing autoimmune diseases, including acceleration of disease progression, overlapping of symptoms and increased diagnostic rates due to heightened health awareness.
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INTRODUCTION

Coronavirus disease (Covid-19) caused by SARS-COV-2 virus has a wide range of presentations and can affect multiple organ systems. The course and severity of Covid-19 vary between individuals and influenced by several factors including the underlying medical conditions and status of the immune system. In the early stages of infection, Covid-19 typically manifests with mild symptoms. However, in some cases, particularly in individuals with immunocompromised or dysregulated immune systems, the disease can progress to severe pulmonary manifestations and multi-organ failure. This progression is often driven by an overactive immune response, leading to excessive inflammation and tissue damage. Beyond the acute phase, Covid-19 has also been associated with long Covid, a condition that poses diagnostic challenges due to its diverse clinical presentations and variable timeline of onset. Reinfections with SARS-COV-2 virus are possible and often result in mild Covid-19, though severe cases can also occur. However, the underlying causes and risk factors of Covid-19 reinfection are not yet fully understood.

The Covid-19 pandemic has not only reshaped the global health landscape but has also led to new insights into the complex interactions between viral infections and the immune system. The impacts and potential links of Covid-19 with immune conditions, including autoimmune disease has been of interest in the scientific community. Covid-19 may trigger immune dysregulation that can exacerbate pre-existing autoimmune conditions or potentially initiate autoimmunity in susceptible individuals. Several theories have been proposed to explain the mechanisms underlying these associations. However, understanding these links is challenging, as most autoimmune diseases are complex disorders with underlying mechanisms that remain incompletely understood. Moreover, the clinical manifestations, immune responses and pathogenic mechanisms of Covid-19 are very similar to those of autoimmune diseases, making it difficult to distinguish between Covid-19-related immune symptoms and those of autoimmune diseases (1).

Systemic sclerosis is a rare autoimmune disease as compared to systemic lupus erythematous or

rheumatoid arthritis. The clinical course varies but most patients have a chronic course, characterised by tissue fibrosis, vascular abnormalities and immune system dysregulation. It primarily affects the skin, but it can involve multiple internal organs. Interstitial lung disease (ILD) is one of the major manifestations in both subsets of SSc, namely limited cutaneous SSc and diffuse cutaneous SSc. The aetiology of SSc remains unknown, though genetic, environment and immune-related factors are believed to contribute to its pathogenesis. The pathogenesis involves abnormal activation of fibroblasts and excessive production of collagen and extracellular matrix, leading to dysfunction in affected organs (1).

Since 1980 there were many criteria to diagnose SSc. However, the 2015 guidelines from the American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) have made the diagnosis of SSc more directed by establishing specific criteria with different score weights (2). We present the case of a woman with a history of Covid-19 reinfection, who presented with symptoms suggestive of long Covid five months after her second infection. Further medical evaluation led to a diagnosis of limited cutaneous SSc, revealing that the disease course had likely progressed prior to her Covid-19 infection, but had gone undetected. This case highlights the potential impacts of Covid-19 on pre-existing autoimmune diseases, with a specific focus on SSc.

CASE REPORT

A 49-year-old Malay housewife with underlying dyslipidaemia and a history of Covid-19 reinfection was referred to the Rehabilitation Department for long Covid rehabilitation programme, five months after her second infection. She had her first Covid-19 infection in July 2021, during which she required a bilevel-positive airway pressure (BiPAP) for one week. She was discharged with oral steroids after ten days of admission. Approximately ten months later, in May 2022, she had another Covid-19 infection, presenting with only mild symptoms and managed through home quarantine. Her lowest oxygen saturation recorded at home was between 89% and 90%, however, she did not seek medical attention.

One month following her second Covid-19 infection, the patient developed a persistent dry cough. A tuberculosis workout was conducted, yielding negative results. Additionally, she experienced an unintentional weight loss of approximately 10kg over the course of one year, associated with a significant loss of appetite. Since her initial Covid-19 infection, she had also been experiencing exertional dyspnoea, easy fatiguability, weakness of the right hand, multiple joint pain and memory impairment.

Further history revealed that she had experienced swelling of all fingers that associated with weakness, numbness and pain for the past five years. Pain was reported in all the joints of bilateral fingers, wrists, elbows, knees and ankles, with occasional exacerbations occurring in the early morning and during exertion. She denied any history of trauma or falls. The patient noted that occasionally her fingers turned bluish upon exposure to cold, and she observed skin changes on her face and bilateral upper limbs after beginning her work as a gardener in 2018. She had no family history of connective tissue disease or skin disorders.

On lung auscultation, reduced air entry was noted in bilateral lower lungs. Hand examination revealed swollen fingers that were warm to touch. Her skin was tight from the distal fingers up to the elbows, and there were hypopigmented patches on her face, upper limbs and back. Raynaud phenomenon was not observed during the examination. A six-minute walking test demonstrated a decline in oxygen saturation from 93% to 86% after 126 meters of walking under room air. Her peaked expiratory flow rate (PEFR) was 300L/min.

Due to her symptoms, an autoimmune workout was done (Table I). Her antinuclear antibody (ANA) was positive for homogenous pattern with titre >1:640. Anti-double-stranded DNA (dsDNA) was negative. Extractable nuclear antigen (ENA) was positive for anti-Scl-70 (Figure 1). Skin biopsy from the hypopigmented area was reported as increased dermal collagen thickening extending to subcutaneous tissue with preserved skin adnexa but reduced peri-eccrine fat (Figure 2). Immunofluorescence study of the skin sample, however, was inconclusive. Both symptoms and investigations were suggestive of SSc.

Table I: Summary of patient's blood investigations.

Indices	Value	Normal value
Haemoglobin (g/dL)	13.3	11.5 - 15.5
White blood cell ($x10^9$/L)	9.14	5.00 - 13.00
Platelet ($x10^9$/L)	387	170 - 450
Erythrocytes Sedimentation Rate (mm/hr)	67	0 - 10
C-Reactive Protein	4.8	-
Sodium (mmol/L)	136	136 - 145
Potassium (mmol/L)	4.3	3.5 - 5.1
Urea (mmol/L)	5.0	3.2 - 8.2
Creatinine (umol/L)	56	62 - 115
Albumin (g/L)	43	32 - 48
Aspartate Transaminase (U/L)	24	0 - 34
Alkaline Phosphatase (U/L)	86	46 - 116
Alanine Transaminase (U/L)	50	10 - 72
HBsAg	Non-reactive	-
Anti-HCV	Non-reactive	-

CONTINUE

Table I: Summary of patient's blood investigations. (CONT.)

Indices	Value	Normal value
HIV-Combo	Non-reactive	-
Syphilis serology	Non-reactive	-
Rheumatoid factor	Negative	-
Anti-CCP	Negative	-
C3 (g/L)	1.56	0.96-1.74
C4 (g/L)	0.41	0.19-0.47
Anti-nuclear antibody (ANA)	ANA Screening: Positive ANA Pattern: Homogenous Titre >1:640	-
Anti-double-stranded DNA	Negative	-
Extractable nuclear antigen (ENA)	Positive anti-Scl-70	-

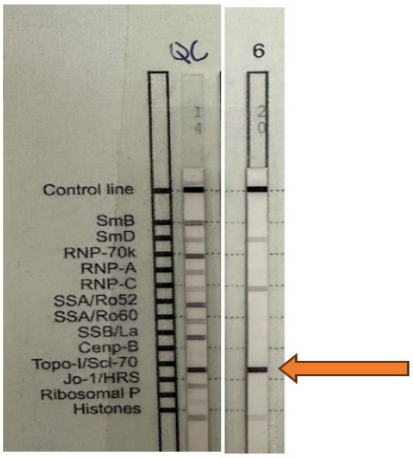

Figure 1: The extractable nuclear antigen (ENA) of the patient (indicated as strip number 6) shows an isolated positive line for anti-Topo-I/Scl-70 (arrow) by an immunoblot test method.

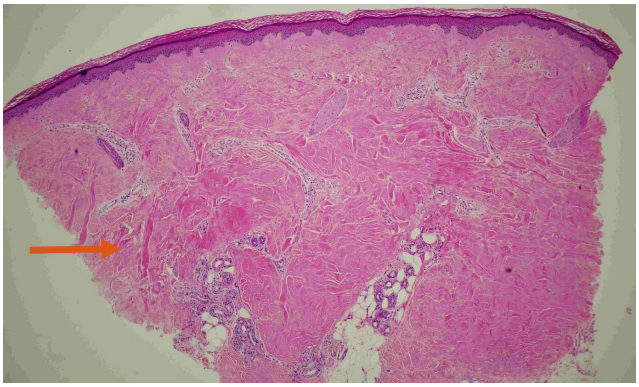

Figure 2: Skin biopsy shows thickening of dermal collagen extending until subcutaneous layer (arrow) indicating excessive production of collagen in the skin.

During her hospital stay, the patient experienced recurrent episodes of dyspnoea, particularly on exertion, requiring the use of a nasal cannula. A high-resolution computed tomography (HRCT) scan of the thorax was performed to rule out fibrosis or ILD following her Covid-19 infections. The imaging demonstrated features of a non-specific interstitial pneumonia pattern with a prominent upper oesophagus which is highly suggestive of autoimmune ILD due to SSc (Figure 3). Her final diagnosis was long Covid with newly diagnosed limited cutaneous SSc.

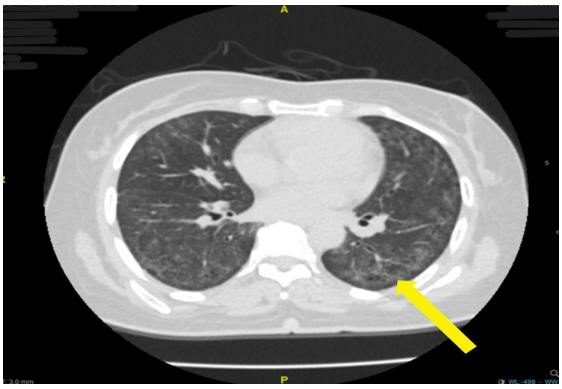

Figure 3: HRCT thorax shows bilateral ground glass densities with emphysematous-like cysts within the densities (yellow arrow) suggestive of non-specific interstitial pneumonia pattern with a prominent upper oesophagus strongly indicative of autoimmune interstitial lung disease due to scleroderma.

In the ward, the patient participated under a pulmonary rehabilitation program that taught on how to perform pursed-lip breathing, deep breathing exercises, endurance training with ambulatory oxygen and pacing techniques. She was also trained on energy conservation techniques, memory training and muscle-strengthening exercises. After eleven days of admission, she was discharged from the rehabilitation ward, having maintained an oxygen saturation level above 92% even during endurance activities under room air. Subsequently, she was referred to the rheumatology team at another facility for further management of SSc and was advised to continue her breathing exercises at home.

DISCUSSION

The role of viral infections in autoimmunity have long been recognised and has been the interest of the scientific community for decades. The Covid-19 pandemic provides a unique opportunity to deepen our understand of this relationship. Several potential mechanisms may link the SARS-CoV-2 virus to autoimmunity. First, molecular mimicry occurs when lymphocyte receptors recognise both self-proteins and foreign antigens due to their structural similarities. This can lead to immune cross-reactivity, which is an important mechanism in the immunopathogenesis of systemic autoimmune rheumatic diseases. Second, neutrophil extracellular traps (NETs) which are released by the neutrophils to combat infections, can also act as a source of self-antigens, potentially leading to the development of autoimmune diseases. Finally, the activation of interferons and cytokines can disrupt immune tolerance in susceptible individuals, further increasing the risk of autoimmunity. These mechanisms may also potentially exacerbate symptoms and accelerate disease progression in individuals with pre-existing autoimmune

disorders (1). The pathogenesis of SSc, characterised by vasculopathy, immune-driven inflammation with cytokine release and organ-specific fibrosis, has also been described in Covid-19. Furthermore, numerous studies have shown that SARS-CoV-2 primarily targets the endothelium – a key mechanism in SSc – suggesting that Covid-19 may accelerate the progression of SSc (3).

In a multicentric retrospective study of 112 patients with pre-existing SSc, 21% experienced an increase in disease activity following Covid-19 infection. These patients presented with progression or new onset of Raynaud phenomenon, digital ulcerations, dyspnoea and cough. In patients experiencing new or worsening dyspnoea, a significant proportion was found to have ILD, suggesting that SARS-CoV-2 infection might exacerbate or trigger lung involvement in individuals with SSc. New-onset dyspnoea was also observed in 20% of SSc patients without ILD, which commonly reported as a symptom of long Covid. This highlights the challenge in determining whether the dyspnoea is a result of Covid-19 or due to a new lung involvement in SSc (3). Notably, another study reported a higher prevalence of Covid-19 among patients with rheumatic diseases including SSc compared to the general population. The prevalence of Covid-19 was also found to be higher in SSc patients with associated ILD than in those without ILD (4). This could potentially explain the increased susceptibility of the patient in our case to Covid-19 reinfection.

The symptoms of Covid-19 and autoimmune diseases such as fatigue, joint pain and dyspnoea, often overlap, making diagnosis more challenging. In current case, having a history Covid-19 reinfection, the patient was initially diagnosed with long Covid and referred to a rehabilitation programme. Only during this referral, she was further investigated for autoimmune connective tissue disease. History taking revealed that swelling of fingers, multiple joint pain and Raynaud phenomenon had been present for five years prior to her first Covid-19 infection. Due to its rarity in general population and its non-specific early signs and symptoms, the patient might have dismissed the clinical manifestations of SSc at that time as something insignificant. Her hand stiffness presented as skin tightness extending from her distal fingers up to the elbow, while the difficulty in breathing was likely due to autoimmune ILD. Her skin biopsy also showed remarkable dermal collagen thickening extending to the subcutaneous tissue. According to (ACR-EULAR) 2015, this patient had a significant skin thickening which is sufficient to establish the diagnosis of SSc. She also had ILD, history of Raynaud phenomenon and a positive anti-Scl-70, which accounted for a total score of seventeen.

Anti-Scl-70, also called anti-topoisomerase I was strongly positive in this patient. Anti-Scl-70 is highly specific for SSc and commonly associated with a positive ANA. The Scl-70 (topoisomerase I) staining appears as obvious fluorescence of the chromosome plate in mitotic cells on ANA indirect immunofluorescence assay. According to International Concessus of ANA Pattern (ICAP), this rare Scl-70 pattern is classified under the expert level recognition and might be misidentified as homogenous pattern by the non-experts. Anti-Scl-70 has a 100% specificity for association with SSc but is only 20% sensitive, making the detection and diagnosis extremely certain.

The pandemic Covid-19 has heightened the public awareness on personal and public health, especially among those who have been infected. Many patients have significantly changed their lifestyles, becoming more attentive to frailty and well-being. In this case, the diagnosis of SSc was discovered following the identification and management of long Covid. The prognosis of SSc patients with Covid-19 is generally good. Studies have found that the underlying comorbidities are significant predictors Covid-19 severity, with mortality rates among this group ranging from approximately 3% to 12% (3,5).

This care report is limited by insufficient clinical information and accessibility to investigation results of the patient both before and after her SSc diagnosis, as she was managed at different health facilities. The information retrieval was also hindered by inefficient hospital information system. We were unable to obtain her previous CT scan taken during her initial Covid-19 admission, which could have provided insights into the progression of her lung condition.

CONCLUSION

This study highlights the impacts of Covid-19 on SSc, with growing evidence of overlapping pathogenesis and clinical manifestation between Covid-19 and SSc. Due to the similarity in clinical features between autoimmune diseases and long Covid, there should be heightened index of suspicion for autoimmune conditions in patients with a history of SARS-CoV-2 infection. Early diagnosis and treatment can lead to better outcomes. As our understanding of Covid-19 and its long-term effects evolves, further research is essential to explore potential

links between viral infections and the acceleration of autoimmune diseases.

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