

Systemic lupus erythematosus manifestation following COVID-19 infection: A coincidental or causal relation

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ABSTRACT

Several intricate interactions of environmental and genetic factors can lead to autoimmune conditions in susceptible hosts. Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease which can be triggered or exacerbated by infection or infectious reactions. The causal link between infections and autoimmunity has been established through clinical studies. Although several viral infections have been associated with SLE, yet the impact of COVID-19 on SLE onset and flares has not been well established. We report a young female who developed new-onset SLE shortly after having COVID-19 infection. Her clinical and lab parameters were highly suggestive of SLE and she responded to standard medical therapy. We also briefly discuss the pathogenetic mechanisms of autoimmunity in cases of viral infections.

Key words: Autoimmunity, Covid-19, Severe acute respiratory syndrome coronavirus 2, Systemic lupus erythematosus

The human body is constantly involved in an intricate interplay with its surrounding natural environment. This dynamic process can consequently lead to a wide range of environmental agents and substances which might benefit, hurt, or even threaten the host life. It is clearly obvious that not everyone reacts or succumbs to these environmental triggers in the same way, which is mainly attributable to the individual genotypic and phenotypic variances and hence variable expression of the response [1]. Thus, environmental factors, specifically, infections and pathogens, which act on the human immune system, can contribute to the onset as well as the severity of autoimmune diseases [1,2]. Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease which can be triggered or exacerbated by infection or infectious reactions [1-4]. The causal link between infections and autoimmunity has been established through clinical studies, proving the role of infectious agents in the induction, as well as in the progression or flareups of SLE [5]. Viral infections such as Epstein-Barr virus (EBV), cytomegalovirus and parvovirus B19, and retroviruses have been found to be implicated in the etiology and pathogenesis of SLE. The impact of COVID-19 on SLE onset and flares has not been evaluated. Recently, however, few reports have been published, showing

the onset of SLE following COVID-19 [6-11]. In this case report, we present a young female who developed new-onset SLE shortly after having COVID-19 infection. We will also discuss the relationship between viruses, particularly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), autoimmunity and SLE.

CASE REPORT

A previously healthy 32-year-old Kenyan woman presented to the emergency department with fever, right shoulder, and wrist pain. She had a history of close contact with her roommate who was recently diagnosed with COVID-19 infection. On examination, her blood pressure, pulse rate, and respiratory rate were stable, and the physical examination was unremarkable. The complete blood count was within normal range, and X-rays for the right shoulder and wrist were unremarkable. The polymerase chain reaction (PCR)-test for COVID-19 was positive. As the patient denied any respiratory symptoms, she was sent home for self-isolation as per the prevalent guidelines.

7 days later, she presented to the hospital with a 5-day history of fever and generalized body aches and pains, especially in her arms and legs, bilateral knee pain and swelling, throat pain, vomiting, and diarrhea. On examination, she had multiple tender joints including shoulders, elbows, a few metatarsophalangeal

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joints, and proximal interphalangeal joints. She also had mild bilateral knee swelling and a non-blanching macular, red-colored rash on her both lower legs. The examination of neurological, cardiac, respiratory, and abdominal systems was unremarkable.

Lab tests showed peripheral cytopenia: Severe leukopenia (white blood cells 2800/ μ L) with marked lymphopenia (Lymphocyte count 500/ μ L), mild neutropenia (ANC 1200/ μ L), moderate microcytic anemia (Hemoglobin 8.5 g/dl, mean corpuscular volume 77.6 fl), along with mild thrombocytopenia (platelet count of 130,000/ μ L) as well as elevated ferritin level (423 ug/l). Furthermore, the C-reactive protein level was elevated (47.1 mg/l). The serum level for thyroid stimulating hormone was elevated at 8.29 mIU/L, while the serum levels of free T4 was normal at 13.9 pmol/L. As per our local protocols, the patient was transferred to a designated COVID-19 hospital facility (Cuban Hospital) for further management. On day 8 after the positive Covid-19 test, a repeat COVID-19 PCR test was done which was negative, and she was referred back to the tertiary center, Hamad General Hospital (HGH), for further treatment of her symptoms.

In the first 6 days, during her stay in HGH she had variable daily spikes of fever ranging from low to high-grade (oral temperature ranging between 38.1°C and 38.6°C). She also reported generalized fatigability and pain in the joints of her upper and lower limbs bilaterally. She was started empirically on intravenous antibiotics (Piperacillin/Tazobactam) for a total of 7 days. The blood cultures came back negative for any growth.

The pancytopenia persisted and respiratory viral panel PCR test was negative. The direct antiglobulin test was positive and the autoimmune panel was positive for antinuclear antibodies (Titer > 1: 1280). The Anti-dsDNA was also positive while Anti-Ro, Anti-La, Anti Rib-P, Anti-Scl70, and Anti-RNP were negative and the serum complement levels were low. The 24-h urine showed a protein concentration of 0.34 g/day. Based on the European League Against Rheumatism 2019 criteria (fever, arthritis, pancytopenia, positive serology, and low complements), the patient was diagnosed with SLE, which was most likely precipitated by the COVID-19 infection.

She was started on a 3-day course of intravenous methylprednisolone at a daily dose of 500 mg. The patient showed dramatic improvement the very next day. The fever subsided, as did the joint pain and fatigue. She was discharged on oral prednisolone 40 mg/day, with a plan to taper the dosage by 5 mg every week to a daily maintenance *dose* of 5 mg. An outpatient follow-up was also arranged in the rheumatology clinic.

DISCUSSION

The pathogenesis of autoimmune diseases is usually an intricate interplay between environmental factors (including viruses), and genetic components, resulting in an immune response against autoantigens representing a failure of immunologic tolerance [1-5]. A causal link between viral infections and autoimmunity has been studied for a long time and the role of some viruses in the induction or exacerbation of SLE

in genetically predisposed patients has been proved. The predominant pathogens known to be associated with SLE include EBV, parvovirus B19 virus, exogenous retroviruses (e.g., human T-lymphotropic virus type 1 and human immunodeficiency virus type 1), and endogenous retroviruses [5]. Since the declaration of COVID-19 as a pandemic by the WHO on March 11, 2020, some cases of COVID-19-associated SLE including ours have been reported. Some case reports, including ours, described new-onset SLE, either concomitantly or after COVID-19 [6,8,11], whereas others described flare-up of the disease during or after COVID-19 infection. The diagnosis of recent onset or flare-up of SLE can be challenging in patients with COVID-19 because both diseases share some characteristics, such as fever, myalgia, arthralgia, and fatigue. Moreover, pulmonary manifestations are very common in patients with SLE, with 50–70% of patients affected by some form of pulmonary complications throughout their disease. Our case presented with fever, arthralgia, and arthritis, but without respiratory symptoms which makes us to propose the diagnosis of SLE. However, it is unclear whether these SLE events were coincidental or were causally related to COVID-19.

The role of SARS-CoV-2 in the pathogenesis of autoimmune diseases is questionable. However, evidence suggests that some drugs used to treat autoimmune rheumatologic diseases may have therapeutic effects in patients with severe COVID-19 infections, raising the possibility that COVID-19 may play an important contributing role in the pathogenesis of autoimmune diseases. Although at the beginning, there have been substantial scientific efforts around the world to elucidate the role of COVID-19 in the pathogenesis of autoimmune diseases. Recently, it was found that about half of the people hospitalized with severe COVID-19 infection had at least one type of autoantibody circulating in their bloodstream. In contrast, only 15% of healthy controls had such antibodies, whereas another study found that autoantibodies that existed before infection with SARS-CoV-2 may account for 20% or more of serious or fatal COVID-19 cases [12,13]. Moreover, a recent systematic review showed the potential of the COVID-19 virus to trigger a myriad of autoimmune and rheumatic manifestations [14]. However, they failed to link COVID-19 to SLE. On the other hand, some studies have linked coronaviruses with other autoimmune diseases. Joo *et al.* [15] found increased incidence of rheumatoid arthritis (RA) after exposure to respiratory viral infections (including coronavirus, parainfluenza, and metapneumovirus). They concluded that coronaviruses may have the capacity to trigger RA.

There are possibly several mechanisms of autoimmunity following SARS-CoV-2 infection. These include molecular mimicry whereby the viral epitopes cross-react with the host due to structural protein similarity, bystander killing when the virus-specific CD8+ T cells directly lead to the target tissues and cause direct cytotoxicity, epitope spreading and formation of neutrophil extracellular traps. Another possible mechanism could be the *in vivo* persistence of the virus which can potentially cause the activation of polyclonal antibodies due to the sheer persistent presence of viral antigens driving immune-mediated injury [13,14].

CONCLUSION

New-onset SLE or its flare-up should be considered and looked for in patients with COVID-19 infection who predominantly present with rheumatic manifestations. However, it is too early to come up with a conclusion, as we may be just at the start of learning phase about a possible link between SLE and COVID-19 infection. Future scientific studies and clinical research is warranted to elucidate this question in order to support or refute this hypothesis.

AUTHORS CONTRIBUTION

Hajmusa M is a member of the treating team who contributed to writing the manuscript and reviewing the literature. Akbar RA is the team leader who contributed to developing the work idea and composing and revising the manuscript.

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