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Journal of Mosaic of Autoimmunity
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Communication

COVID-19 and Systemic Lupus Erythematosus

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How To Cite: Athanassiou, L.; Kostoglou-Athanassiou, I.; Kaiafa, G.; et al. COVID-19 and Systemic Lupus Erythematosus. *Journal of Mosaic of Autoimmunity* **2025**, *1* (1), 4.

Received: 2 January 2025
Revised: 17 February 2025
Accepted: 27 February 2025
Published: 3 March 2025

Abstract: Viruses may be involved in the pathogenesis of autoimmune diseases. In particular, the viral etiology of systemic lupus erythematosus (SLE) has been discussed and extensively investigated. Epstein Barr virus may be implicated in the pathogenesis of SLE. The SARS-CoV-2 virus has been implicated in the pathogenesis of autoimmunity. The COVID-19 infection has been associated with the development of subacute thyroiditis, diabetes mellitus type 1, rheumatoid arthritis, ankylosing spondylitis and SLE. The case of a female patient is described who developed fatigue, arthralgias, edema, joint pain and a generalized skin rash following a mild COVID-19 infection. Laboratory investigations were compatible with SLE. In conclusion, the case of a patient is described who developed SLE after a mild COVID-19 infection. This case shows that the SARS-CoV-2 virus may cause autoimmunity and that viruses may be implicated in the pathogenesis of systemic autoimmune diseases.

Keywords: SARS-CoV-2, COVID-19, systemic lupus erythematosus, autoimmunity

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune diseases [1,2]. It affects all organ systems and has a variable course and prognosis [3]. The disease may affect the kidneys and the central nervous system and impacts significantly quality of life [4,5]. The etiology of SLE has been extensively investigated [6]. Various agents have been implicated, amongst those viruses and ultraviolet light [7]. It appears that environmental agents such as viruses act in the presence of a permissive genetic background and defective clearance pathways and induce SLE (Figure 1) [8]. The infectious etiology of SLE has attracted scientific interest [9,10]. In particular, viruses have been discussed as etiologic factors leading to the development of SLE (Figure 2) [11–13]. The Epstein Barr virus has been investigated as a possible inducing factor for SLE [14–16]. The virus affects all humans early or later in their life [17,18]. It causes cancer and the infectious disease infectious mononucleosis [19,20]. However, it remains in a latent state in human cells and may revert to a lytic state in cases of an intervening infection or a stressful event [18]. The virus infects B lymphocytes [20], and may remain within the nucleus of these cells as an episome, shifting between a latent and a lytic phase. The Epstein Barr virus has been related to the development of autoimmunity, in particular multiple sclerosis and SLE [14,21]. The SARS-CoV-2 is an "autoimmune" virus, i.e., a virus related to the development of autoimmunity. This idea was suggested at first by Shoenfeld et al. [22] as the pandemic swept over humanity causing thousands of deaths. This idea was based on the presence of molecular mimicry between similar motifs of amino acids present in viral and human proteins, hyperstimulation of the immune system by the virus and the development of excessive extracellular neutrophil traps. As the infectious disease has now affected all nations world-wide, descriptions of the

development of meta-inflammatory and autoimmune diseases, such as subacute thyroiditis [23–27], diabetes mellitus type 1, rheumatoid arthritis [28–30], ankylosing spondylitis [31,32] and SLE emerged. An increase in the incidence of type 1 diabetes mellitus was noted following the SARS-CoV-2 infection [33]. In Colombia an increase in the incidence of rheumatoid arthritis was described following the COVID-19 pandemic [30]. Zheng [34] described the emergence of ankylosing spondylitis specific T cells following COVID-19 infection.

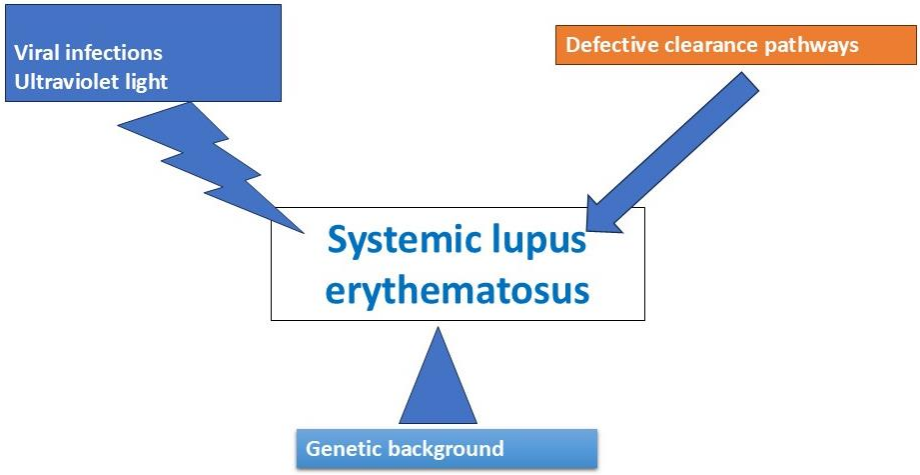

Figure 1. The pathogenesis of systemic lupus erythematosus.

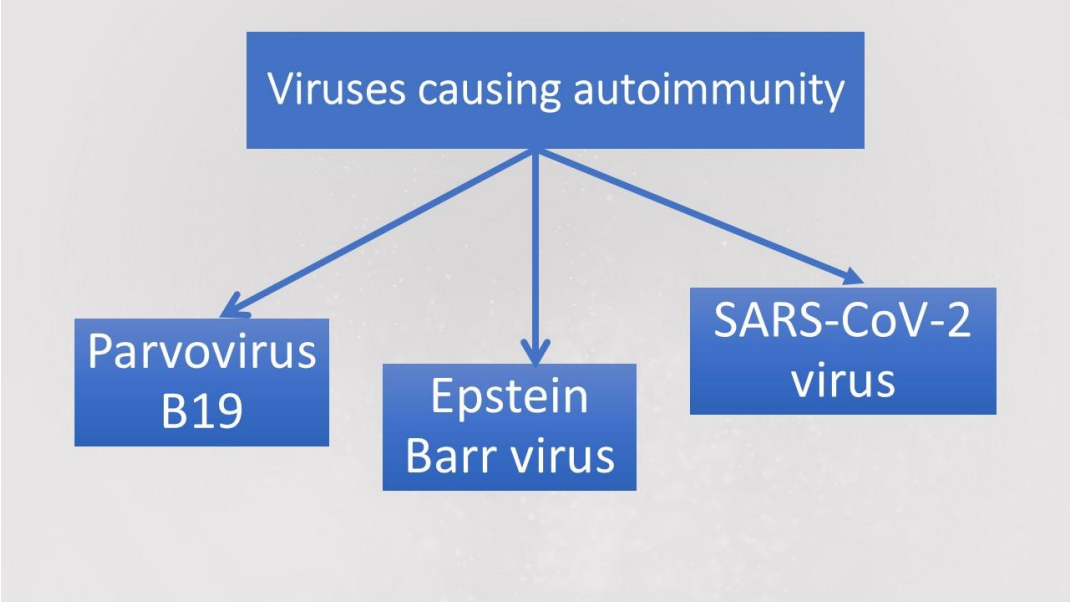

Figure 2. Viruses cause autoimmunity.

We describe the case of a 51-year-old female patient who developed SLE 10 days after a mild COVID-19 infection, characterized by fever up to 38.5 °C and cough. The patient developed fatigue, arthralgias, morning stiffness, edema and pain in the knee joints and a generalized skin rash. Laboratory investigations revealed ANA (Hep2) 1/320 positive, anti-ds-DNA 1/40 positive (normal values ≤ 1/10), anti-Sm 22.6 u (<20 u), anti-SS-A(Ro) 131.5 u (<20 u), anti-SS-B(La) 76.6 u (<20 U), anti-RNP 33.5 U (<20 u), anti-Scl 70 negative, EBV IgG 48.86 positive and EBV IgM 0.01 negative. Leukopenia was observed, white blood cells 2.92 × 10^3/μL. Hydroxychloroquine, azathioprine and belimumab were sequentially administered with partial response. Prednisolone was administered orally, at a dose of 15 mg daily which was subsequently decreased to 12.5 mg daily, and the patient improved significantly. The patient was followed for a period of 18 months. Symptoms improved, however, arthralgias and pain in the knee joints persisted. The patient did not complain about xerophthalmia or xerostomia and did not have parotid gland enlargement.

The SARS-CoV-2 virus may induce the development of autoimmune diseases [22] (Figure 3). Bonometti et al. [35] described a case of SLE induced by COVID-19 infection. The case of a previously healthy patient who developed SLE with antiphospholipid syndrome and a rash involving the trunk leading to a fatal outcome has been

reported [36]. Development of new onset SLE with antiphospholipid antibodies and deep venous thrombosis concomitantly with a SARS-CoV-2 infection was described in an 18-year-old female patient [37]. Development of lupus nephritis in a patient with SLE in the context of mixed connective tissue disease following a COVID-19 infection has been observed [38]. New onset lupus nephritis following a SARS-CoV-2 infection in a male patient has been reported [39]. The development of lupus nephritis following a mild SARS-CoV-2 infection [40], in the case of a male patient with acute renal failure one month after the infection has been observed [41]. In a German study based on insurance data involving 641,407 individuals with molecularly confirmed COVID-19 disease and 1,907,992 control subjects with a period of follow-up of 3 to 15 months the excess risk for any new diagnosis of autoimmune disease was 4.5 per 1000 person-years [42]. In the aforementioned study a 42.63% higher likelihood of acquiring an autoimmune disease was noted in the group who had suffered a COVID-19 infection as compared to the control group. In this same study the incidence rate ratio for SLE was 1.34 with a 95% CI of 0.92–1.95 for individuals who had a prior SARS-CoV-2 infection as opposed to the control group. In a British study performed in the UK a 22% increased risk of developing an immune mediated inflammatory disease was noted in a cohort exposed to the SARS-CoV-2 virus as opposed to a control group [43]. In this study the incidence of type 1 diabetes mellitus, inflammatory bowel disease and psoriasis was found to be increased in relationship to exposure to the SARS-CoV-2 virus. In a retrospective study based on data derived mainly from the US population estimating the risk for autoimmune diseases after a SARS-CoV-2 infection, an increased risk for the development of all autoimmune diseases including SLE and mortality from those diseases was observed in the COVID-19 survivors as opposed to the control population [32]. In this study the adjusted hazard ratio for SLE in the COVID-19 survivors was 2.99 with a 95% CI of 2.68–3.34. The development of SLE and SLE with lupus nephritis following vaccination against COVID-19 has also been reported [44,45]. The development of ASIA syndrome, i.e., the autoimmune/autoinflammatory syndrome induced by adjuvants or Shoenfeld's syndrome has also been described in relationship to the COVID-19 vaccine [46]. In addition, the SARS-CoV-2 infection may induce a flare in some SLE patients [47]. The patient described herein fulfilled the criteria for the diagnosis of lupus and had anti-Sm antibodies which are lupus characteristic [48].

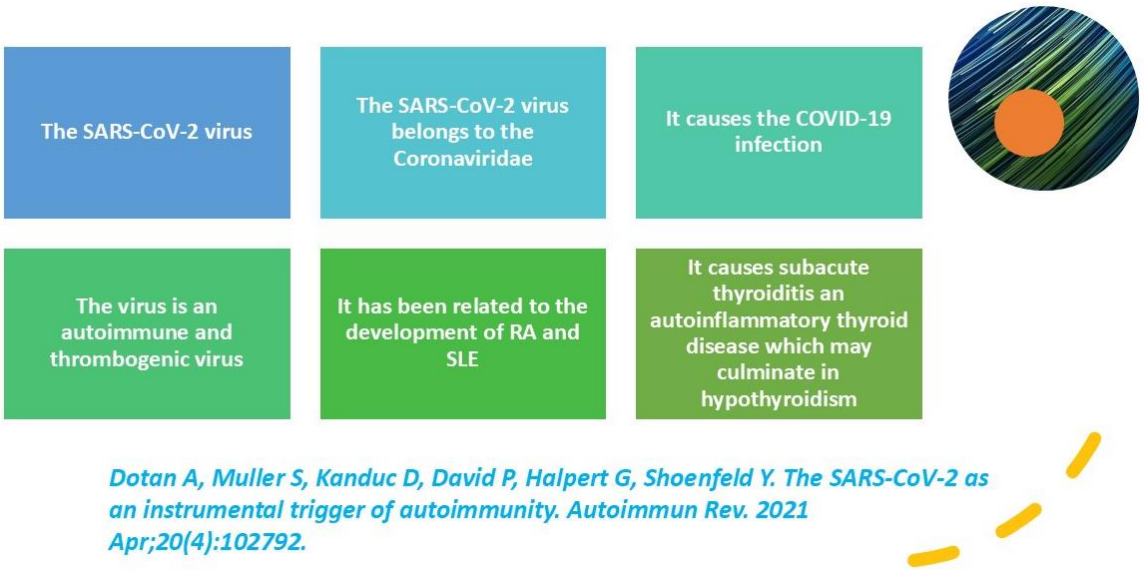

Figure 3. The SARS-CoV-2 virus [22].

In conclusion, infection from the SARS-CoV-2 virus may lead to the development of autoimmune diseases including SLE. SLE after COVID-19 infection may respond favorably to corticosteroids.

Take home messages

- The case of a patient is described who developed SLE following a subclinical COVID-19 infection.
- This case shows that the SARS-CoV-2 virus is related to the development of autoimmunity.
- It is another case depicting the potential of viral infections to cause systemic autoimmunity.

Author Contributions

L.A.: conceptualization, methodology, software; I.K.A.: conceptualization, data curation, writing—original draft preparation; G.K.: visualization, investigation, methodology; C.S.: supervision, investigation, methodology;

P.A.: conceptualization, methodology, software, validation; Y.S.: conceptualization, validation, writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data are available at the database of Asclepeion Hospital, Voula, Greece.

Conflicts of Interest

The authors declare no conflict of interest.

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