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Case Reports

A case of C-ANCA positive systematic lupus erythematous and ANCA-associated vasculitis overlap syndrome superimposed by COVID-19: a fatal trio

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Running Head: SLE/AAV overlap syndrome and COVID-19

Abstract:

Coronavirus disease 2019 (COVID-19) possesses a substantial challenge for rheumatologists and rheumatologic patients. They are concerned about the reciprocal interaction between connective tissue diseases, such as systemic lupus erythematosus (SLE), and the virus. Here, we report a 21-year-old female SLE patient presented to the emergency department with gastrointestinal symptoms and kidney involvement evidence. Based on the pathology and laboratory assessments, she was suspected of C-anti-neutrophil cytoplasmic antibody (ANCA) positive SLE and ANCA-associated vasculitis overlap syndrome (SLE/AAV OS), and plasmapheresis every other day was performed due to this diagnosis alongside the high titer of C-ANCA. We also administered methylprednisolone (1 g/day, IV) for

three days, followed by dexamethasone with the maintenance dosage (1mg/kg/day, IV). Although the patient's general condition improved the next days, her condition deteriorated suddenly on the 7th day of hospitalization. She got intubated and went to the intensive care unit. Despite taking possible measures to manage the patient's condition, she eventually passed away due to severe acute respiratory distress syndrome (ARDS), triggered by COVID-19. The distinct role of C-ANCA in SLE/AAV vascular damage and activating neutrophil cytokine release accompanied by the impaired immune system while facing COVID-19 seems to lead to increased morbidity and mortality in such patients. This report was presented to bring into consideration the possible role of C-ANCA in the burden and prognosis of COVID-19 in SLE/AAV OS patients.

Keywords: COVID-19, Systemic Lupus Erythematosus, Vasculitis, Anti-neutrophil cytoplasmic antibody, ANCA-Associated Vasculitis

Introduction

The current pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have made rheumatologists concerned about patients' reactions to coexisting conditions, such as systemic lupus erythematosus (SLE) and other chronic collagen vascular disease confronting this debilitating respiratory virus. The rapid spread of the virus worldwide with a growing mortality rate has become an alarming sign. Notably, patients with connective tissue disease taking immunosuppressive agents might be more susceptible to severe forms of COVID-19 **[1]**. SLE is generally known by autoimmunity, which can be related to the increased susceptibility to infections [2]. However, there still exists much controversy over the impact of SLE and COVID-19 coincidence in such patients. On the other hand, the association between COVID-19 and an overt inflammatory response due to severe cytokine release suggests that immunosuppression might modulate this infection's inflammatory response (1). Thus, studies indicate that it would be better to maintain the treatment regimen in SLE patients to avoid SLE flare-ups during the COVID-19 pandemic.

SLE anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis overlap syndrome (SLE/AAV OS) is a recently reported entity in the literature. It is characterized by antinuclear antibody (ANA)'s positive activity plus ANCA, accompanied by arthritis, cytopenia, pulmonary hemorrhage, interstitial pneumonia, cutaneous involvement, and kidney involvement hematuria, proteinuria, and even rapid progression to crescentic glomerulonephritis [3-5].

These complications are believed to be triggered by neutrophils cytokine release mechanism activated by ANCA, including MPO-ANCA (P-ANCA) or PR3-ANCA (C-ANCA), leading to endothelial damage in different organs [6]. Herein, we aimed to report a fatal case of C-ANCA positive SLE/AAV OS superimposed with COVID-19.

Case presentation

A 21-year-old female, known case of SLE from 8 months ago in the outpatient setting, presented to the emergency department with increasing periumbilical pain and a recurrent non-massive watery diarrhea initiating four days earlier. The patient also suffered nausea, vomiting, fatigue, exacerbated headache, and photosensitivity initiated approximately a week before the admission. Besides, her symptoms were gradually accompanied by elevated blood pressure (BP) and serum creatinine level, based on her outpatient follow-ups, suggestive of probable SLE flare-up. Upon arrival, physical findings were as follows: malar rashes on the face, pale palpebral conjunctiva, two ulcers on the palate, and a bilateral mild (1+) pretibial edema. Her BP was 170/120 mm Hg, and the body temperature was 36.5 °C. In addition, a diffuse fine crackle in both lungs could be heard, and the saturation of peripheral oxygen (SPO_2) was 97% in the room air. Abdominal examination revealed no sign of tenderness, rebound tenderness, guarding, or organomegaly. With regards to the patient's SLE background, she had initial signs and symptoms about one year prior to presentation, including malar rash, transient oral ulcers, arthralgia, and abnormal laboratory findings were consistent with SLE diagnosis about 8 months before being referred to our center. Subsequently, she went under treatment with hydroxychloroquine (400 mg/day), and prednisolone (PSL, 10 mg/day). Her serum creatinine level was reported previously to be near normal in the early stages (1.3 mg/dL); however, she developed a gradually increasing lower extremities edema and rised creatinine levels over her routine outpatient follow-ups and mycophenolate mofetil (MMF) (2 g/day) was added to her treatment regimen since 3 months ago. The patient eventually was reffered to our center with an uncotrolled and flared-up SLE.

Laboratory assessments at this center revealed an elevated serum creatinine level and blood urea nitrogen, a high titer of ANA, positive anti-dsDNA IgG, decreased serum levels of complements (C3 and C4), and a extremely high titer of C-ANCA. Details on laboratory tests are reported in Table 1 and

Table 2. Furthermore, granular casts, RBC casts, proteinuria (3960 mg/day), and microscopic hematuria were detected in the 24h urine sample. Besides, a recently performed kidney biopsy in another center reported a diffuse proliferating and sclerosing lupus nephritis class IV-G, endocapillary hypercellularity, and cellular crescents in the majority of glomeruli with immune complex depositions along glomerular basement membrane and mesangium, including IgA (weakly), IgG, IgM, C1q, and C3c. Of note, fibrinogen deposition was not found, while mild hyaline arteriolopathy and focal fibrinoid necrosis in some interlobular vessels as well as vasculitis of extraglomerular vessels were also found. The above-mentioned histopathological findings were consistent with the possible diagnosis of microscopic polyangiitis (MPA), a subtype of AAV; the available digital photos of the patient's histopathological evaluations are provided in Figure 1.

After the initial workup, due to the patient's abdominal pain, gastrointestinal (GI) consultation was performed. The abdominopelvic ultrasonography was reported normal, with particular attention being paid to the kidneys. A subsequent spiral abdominopelvic computed tomography (CT) scan with intravenous (IV) contrast also revealed no evidence of abdominal arteries' involvement suggestive of vasculitis or active SLE. Thus, we related the patient's GI symptoms to the possible common adverse effects of MMF, as a probable diagnosis, and replaced it with a single pulse of cyclophosphamide (750 mg, IV), and treatment with PSL (1 mg/kg of body weight, orally) and hydroxychloroquine (400 mg/day, orally) was continued. We also investigated any possible evidence of anthiphospholipid syndrome in this patient, which was ruled out since no evidence of vascular thrombosis was found in this patient, neither on physical examinations nor on the abdominopelvic contrast CT scan and histopathological evaluations. Specific laboratory tests were also almost normal, as presented in

Table 2. On the other hand, based on the patient's signs, symptoms, and histopathological findings suggestive of vasculitis, SLE/AAV OS was considered as a possible diagnosis. So, we performed plasmapheresis every other day due to this diagnosis alongside the high titer of C-ANCA. We also administered methylprednisolone (1 g/day, IV) for three days, followed by dexamethasone with the maintenance dosage (1 mg/kg/day, IV).

During the first few days of treatment, her general condition was improved, abdominal pain was resolved, serum creatinine level and BP returned to near normal. However, intermittent coughs and mild dyspnea were added to the patient's symptoms, and on the 7th day of hospitalization, the patient suddenly deteriorated and developed new-onset generalized seizures and fever (38°C). Her SPO_2 level fell to 88%, and her dyspnea worsened. Therefore, we initiated empirical therapy with acyclovir, intravenous antibiotics (meropenem, vancomycin) to cover any probable encephalitis, alongside fluid therapy and oxygen therapy. At this point, leukocytosis was observed during further investigations, and the chest x-ray demonstrated extensive lung opacities without any evidence of nodules or cavitations. Chest CT scan (with/without contrast) excluded SLE pneumonitis while showing peripheral bilateral diffuse ground-glass opacities (GGOs), distributed in both upper and lower lobes of the lungs (

Figure **2**). Electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain (with/without contrast) were all clear. Following evaluations for any bacterial infection source, all cultures (blood, urine, and stool) were reported negative.

According to the workups and the GGO pattern on the chest CT scan, the patient was suspected of COVID-19, and the real-time polymerase chain reaction (RT-PCR) assay was tested positive, which suggested a superimposed COVID-19 infection on SLE/AAV. Subsequently, the patient's PSL was tapered, and 20 gr/day of IV immunoglobulin (IVIg) was administered for five days, while other medications were continued. During the next days, she gradually experienced a decrease in consciousness level and delirium. On the 12th day, the patient's Glasgow Coma Scale score (GCS) eventually fell to 8/15, so she was endotracheally intubated, transferred to the intensive care unit (ICU), and the dose of dexamethasone was doubled (2 mg/kg/day). The next day, no significant response was observed, and the patient's SpO_2 fell to 54% despite mechanical ventilation. Ultimately, due to severe acute respiratory distress syndrome (ARDS), the patient passed away on the 14th day—the timeline of the patient's hospitalization period is provided in Figure 3.

Discussion

SLE is a chronic multi-organ autoimmune disease featured by the dysregulated innate and adaptive immune response, multiple autoantibodies, such as ANA and anti-dsDNA antibodies, and complement activation. A group of

autoantibodies called ANCA, that are not supposed to be frequently found in SLE patients, may also be present; however, studies have reported that up to 16% of SLE patients might be ANCA positive, which could be due to and overlaping AAV or as a result of cross-reaction with ANA antibodies [7]. Lupus nephritis (LN) is a renal involvement in SLE mediated by the immune complex, which results in leukocytic infiltration, cellular proliferation, and cytokine release [5]. Our patient was a known case of SLE according to the American College of Rheumatology (ACR) [8], who progressed to class IV-G LN, based on histopathological reports.

AAV, on the other hand, is a necrotizing vasculitis affecting mostly small vessels with few or no immune deposits, accompanied by circulating ANCAs. AAV is mainly categorized into three major groups, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). In the clinical setting, sometimes differentiating these subtypes is controversial, as signs symptoms might overlap [4]. In 2008, Nasr et al. described SLE/AAV OS for the first time since some patients with SLE had positive ANCA tests along with AAV-associated renal pathological findings, including focal and segmental glomerular inflammation and necrosis usually with few or no immune complex deposits [5]. SLE/AAV OS cases are mostly females in whom ANA and ANCA (mostly anti-MPO-ANCA) are positive. Most patients present with complicated manifestations, mainly necrotizing crescentic rapidly progressive glomerulonephritis (RPGN), accompanied by involvement of the GI tract, the lungs, skin, and nervous system in some cases [3,4,6,7]. Our patient also presented with evidence of RPGN based on the clinical and histopathological findings suggestive of a diffuse proliferative and sclerosing glomerulonephritis with evidence of extraglomerular vasculitis as mentioned earlier accompanied by a high titer of C-ANCA activity. According to the Chapel Hill Consensus Conference (CHCC) 2012 and other classification algorithms of AAV [9,10], SLE/AAV OS could be considered in our patient. It is worth noting that ANCA is believed to have a significant role in direct or indirect vascular damage [6], which can also justify our patient's complicated signs and symptoms.

Based on the experience gained from previous studies, there is a great concern that SLE patients might be at increased risk of COVID-19 due to the impaired humoral and cellular immune system parallel to taking extensive immunosuppressive agents, organ damage, and hypercoagulability. In addition, angiotensin converting enzyme 2 (ACE2) is known as a functional receptor for the SARS-CoV-2 spike glycoprotein, and there is evidence showing that in SLE patients, ACE2 could be over expressed on CD4 positive T-helper cells. This can also be another possible mechanism through which SLE patients are at a higher risk of COVID-19 [2,11]. Besides, anti-phospholipid

syndrome is another condition that can put patients at higher risks for severe COVID-19 complications [12,13]. So, we investigated any possible accompaning anti-phospholipid syndrome in our patient, while it was ruled out based on the revised classification criteria [14]. In addition, COVID-19 is known to be associated with a cytokine storm that involves T-helper-1. Cytokine profile analysis of COVID-19 patients has revealed an increased amount of IL-2, IL-7, granulocyte colony-stimulating factor, interferon-γ-inducible protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha, and tumor necrosis factor (TNF)-α. High concentrations of these cytokines in critically ill patients can lead to more severe COVID-19 infections [15,16]. Based on Jennette et al.'s study, ANCA activity could be associated with neutrophil activation and cytokine release [6], which might be a contributing factor to severe infections in COVID-19 patients. The role of immunosupressive therapy on the outcome of COVID-19 is still a matter of controversy based on the existing literature; however, some studies suggest that the administration of corticosteroids and immunosupressive agents might have a beneficial role mitigating both the underlying condition in SLE patients and the COVID-19 associated hyperinflammation. So, it is recommended that these agents be continued in SLE patients during the pandemic to prevent SLE flare or any possible adverse effect due to corticosteroid withdrawal. No doubt, an individualised risk assessment is undeniable for each patient [11].

In summary, our patient was a case of C-ANCA positive SLE presenting with flare-up, LN, and evidence of AAV, manifesting with multi-organ complications. The patient's treatment continued considering SLE/AAV OS as a probable diagnosis, which improved her general condition during the first days. Subsequently, COVID-19 was superimposed on the underlying complications of SLE/AAV and deteriorated the patient's situation. Generally, only a limited number of SLE/AAV OS patients might die out of complications based on previous reports [3]; however, a superimposed condition can worsen the situation, as what happened for our patient. It is worth noting that C-ANCA seems to be a prognostic factor in SLE and AAV patients related to increased mortality and morbidity. Indeed, further studies need to be conducted to clarify C-ANCA's possible role in SLE/AAV patients' prognosis. Correspondingly, all these conditions can induce a cascade of inflammatory processes by themselves, which can exacerbate each other and lead to an uncontrollable fatal condition. So, it would be of great importance to control any underlying inflammatory status of patients, especially during the COVID-19 pandemic, which nessecitates tight follow-up visits and precise adjustments of the treatment regimens and modalities to prevent any possible flare-up.

Patient Consent

Written consent around the permission on presenting this patient was obtained from relatives, as the reported patient passed away.

Acknowledgments

This case report was published with a written consent of the patient's relatives. Besides, this case report was approved by the Qom University of Medical Sciences and Health Services' Research and Ethics Committee.

Conflicts of Interest

None to declare.

Funding Details

None to declare.

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Table 1. Initial laboratory tests of the patient

Item	Result	Normal Range
White blood cells (10^3/L)	14.3	3.4-9.6
Mean corpuscular volume (FL)	78.5	80-95
Hemoglobin (gr/dL)	10.2	11.6-15
Platelets (10^3/L)	234	157-371
Serum Creatinine (mg/dL)	2.9	0.8-1.3
Blood urea nitrogen (mg/dL)	245	8-21
Na (mEq/L)	138	135 to 145
K (mEq/L)	6.4	3.6 to 5.2
Calcium (mg/dL)	8.9	8.6-10.3
Albumin (g/dL)	4.3	3.4 to 5.4
VBG		
PH	7.2	7.35 to 7.45
PCO_2 (mmHg)	22.5	35 to 45
HCO_3 (mmol/L)	10.4	22-26

VBG: Venus blood gas; PCO_2: Partial pressure of carbon dioxide; HCO_3: Bicarbonate

Table 2. Specific immunologic tests of the patient

Item	Result	Normal Range
Complement component 3 (mg/dl)	35	Adult 90-180
Complement component 4 (mg/dl)	7	Adult 10-40
CH50	42 %	51-150%
Antinuclear antibody	1:640	≤ 1:40
Anti-dsDNA IgG (IU/ml)	876	Positive >75.0
Anti-Smith antibody (IU/ml)	4	Positive > 7
PR3-ANCA/C-ANCA (IU/ml)	340	Positive > 20
MPO-ANCA/P-ANCA (IU/ml)	2.1	Positive > 20
Fluorescent antinuclear antibody (Titer)	1:1000	Positive>1:320
Fluorescent antinuclear antibody Pattern	Granular	-
Anticardiolipin IgG (U/ml)	11	Positive > 10
Lupus anticoagulant (DRVVT ratio)	0.70	0.90-1.10
Beta 2 Micro globulin (mg/l)	8.1	0.8 -2.1
Beta 2 Glycoprotein IgM test (U/ml)	0.7	Positive > 18
Beta 2 Glycoprotein IgG test (U/ml)	0.48	Positive > 18
Immunoglobulin G (mg/dl)	1,180	550-1900
Immunoglobulin A (mg/dl)	424	60-350
Immunoglobulin M (mg/dl)	98	50-150
VDRL test	Non-Reactive	-

CH50: total hemolytic complement; DRVVT: Dilute Russell viper venom time (DRVVT)

Figure Legends

Figure 1. Serial sections of kidney needle biopsies were performed for the patient in the outpatient setting, stained with (A) hematoxylin-eosin stain (H&E), (B) periodic acid-Schiff (PAS), and (C) Masson's trichrome, which have been illustrated at ×200 magnification. Based on the accompaning histopatholical reports provided by an expert pathologist, smaples showed diffuse proliferating and sclerosing lupus nephritis class IV-G along with crescent formation. Sections show endocapillary hypercellularity, subendothelial hyaline deposition, and cellular crescents (B, yellow arrows point to the crescents) in the majority of glomeruli, while glomerular fibrosis was observed by Masson's trichrome staining (C, yellow arrow). Foci of karyorrhexis and leukocytic infiltration were evident in the slides. Fibrinoid necrosis was also present in glomeruli (A, yellow arrows), and some tubules contained RBCs and RBC casts. Mild hyaline arteriolopathy and focal fibrinoid necrosis in interlobular vessels were found as well.

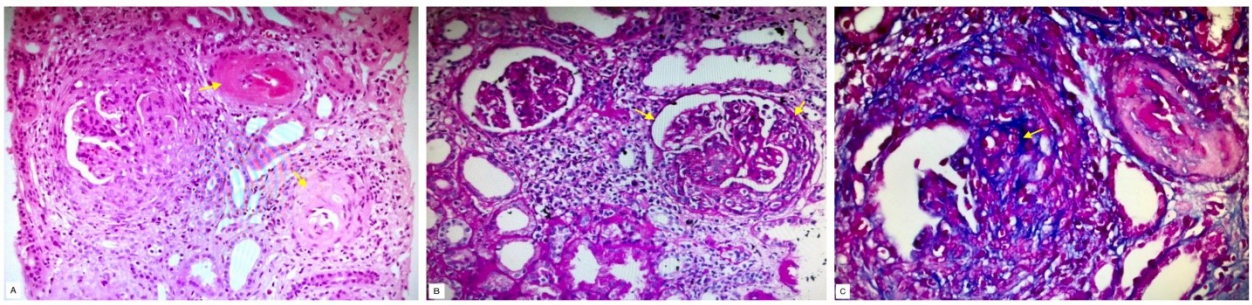

Figure 2. The chest computed tomography (CT) scan showed peripheral bilateral diffuse ground-glass opacities (GGOs) distributed in both the upper and lower lobes of the lung.

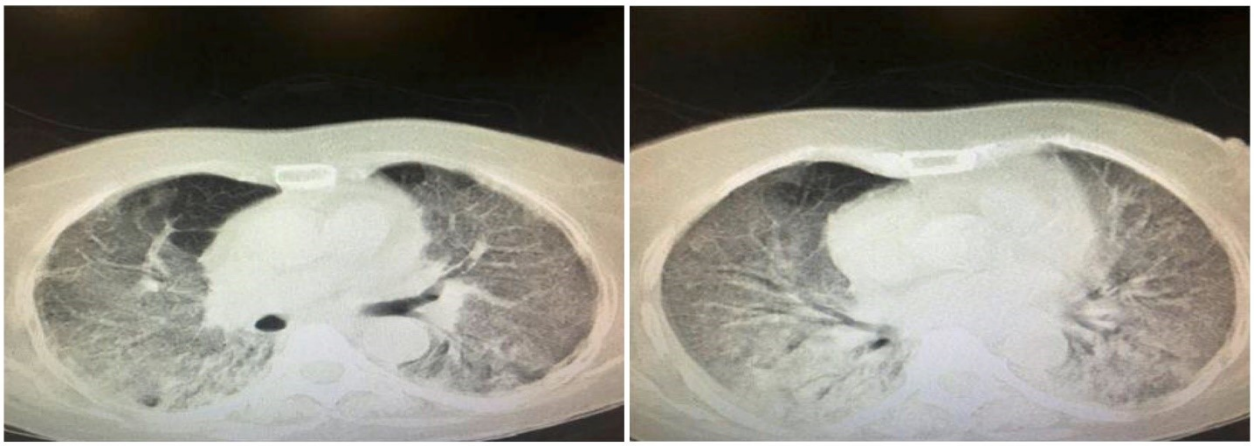

Figure 3. Timeline of the hospitalization period, demonstraiting main investigations, key findings, and treatment measures. BP: Blood Pressure; BUN: Blood Urea Nitrogen; Cr: Serum Creatinine; SLE: Systemic Lupus Erythematosus; AAV: ANCA-Associated Vasculitis; ANCA: Antineutrophil Cytoplasmic Antibodies; Body T: Body Temperature; SPO_2: Oxygen Saturation; PSL: Prednisolone; HCQ: Hydroxychloroquine; MMF: Mycophenolate Mofetil; IVIG: Intravenous Immunoglobulin; ICU: Intensive Care Unit; GCS: Glasgow Coma Scale; ARDS: Acute Respiratory Distress Syndrome; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging.