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Coronavirus Disease 2019 Infection in a Gitelman Syndrome Patient

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To the Editor:

The coronavirus disease 2019 (COVID-19) pandemic has brought attention to the renin–angiotensin system (RAS), specifically angiotensin-converting enzyme 2 (ACE2), as an entry point for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[1] The SARS-CoV-2 virus binds to its target cell via a surface spike protein that binds to ACE2, followed by fusion of the host cell membrane with the viral envelope through the action of specific proteases. After binding of the spike protein and subsequent downregulation of ACE2, it exposes the host cell to severe damage through the pathological effects of RAS deregulation.[2] Patients with Gitelman syndrome (GS) have rare genetic tubulopathies with endogenously elevated levels of ACE2 and angiotensin (1-7). It is therefore possible that this rare tubulopathy may have a protective effect against COVID-19.[3] This is the first case of GS with COVID-19 reported in the literature from Türkiye.

A 26-year-old female patient with GS presented to our outpatient clinic complaining of sore throat, cough, and fatigue. At the time of admission, her vital signs were stable, and no abnormalities were noted on physical examination except for a hyperemic oropharynx. She was taking spironolactone 25 mg, potassium citrate, potassium bicarbonate, and magnesium oxide 365 mg. Real-time polymerase chain reaction was positive. She was hospitalized for severe hypokalemia and hypomagnesemia. Informed consent was obtained from the patient who agreed to take part in the study. The patient had not been vaccinated against COVID-19 and refused specific treatment. The diagnosis of GS was made 9 years ago on the basis of clinical and laboratory data. Therefore, a genetic mutation study was performed; a homozygous c.513del p.Trp172Glyfs*10" mutation in the SLC12A3 gene was detected. After supportive treatment, she was discharged.

The RAS was not only an integral part of the SARS-CoV-2 infection process throughout the pandemic but was also observed to play an important role in lung injury, which is a major cause of morbidity and mortality in COVID-19. Pretreatment with captopril or candesartan prevented SARS-CoV-2 spike protein internalization into human type II pneumocytes and the spike protein-induced proinflammatory cytokine response in a rat lung study, and 3-week treatment with captopril or candesartan was shown to upregulate ACE2 in the rat lung. In addition, reversal of RAS dysregulation by captopril or candesartan in lung tissue from aged rats and rats with metabolic syndrome provided evidence that ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are protective against SARS-CoV-2 infection, confirming that ACEIs and ARBs contribute to reduced viral entry and reduced proinflammatory cytokine release.[4]

A cohort study of 128 GS and Bartter syndrome patients living in northern Italy found that none of the patients were affected or showed symptoms associated with this infection during the first wave of COVID-19 in 2020. When the third wave of COVID-19 occurred, a second study was initiated in the same cohort, and only 8 out of 128 patients were positive for COVID-19, of which 4 were slightly more severe.[3] In these same cohort studies, it was thought that COVID-19 disease was a natural protective effect of high ACE2 levels in cases with GS against the disease. In addition, there is no other study in the literature of patients with GS diagnosed with COVID-19.

Monoclonal antibodies, antiviral agents such as remdesivir, molnupravir, and ritonavir, and vaccines have been proposed as effective treatment strategies and preventive measures.[5] As seen in animal studies,[4] using ACEIs or ARBs in COVID-19 patients has positive effects on the prognosis of the disease, and considering the possible side effects that may develop with the newness of other drugs, very low doses of ACEIs or ARBs can be given in Gitelman syndrome cases, especially by paying attention to the blood pressure of the patients.

In summary, this is the first case of GS diagnosed with COVID-19 in Türkiye. The fact that this is the first case may be explained by the protective mechanism observed in COVID-19 patients with GS due to high levels of ACE2 and angiotensin (1-7) which may favorably affect disease progression. Low-dose ACEIs or ARBs can be given both to GS patients with COVID-19 and other COVID-19 patients.

Informed Consent: Informed consent was obtained from the patient who agreed to take part in the study.

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Immunofluorescence Negative Bullous Pemphigoid in a Hemodialysis Patient with Recurrent Ischemic Stroke

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DESCRIPTION

A 62-year-old male with diabetic nephropathy on maintenance hemodialysis twice weekly with a history of recurrent ischemic stroke in June 2022 and August 2022 presented with right hemiparesis on November 10, 2022. He was on sustained release nifedipine and carvedilol for his blood pressure and received pregabalin for his chronic pruritis. His parathyroid hormone (PTH) in September 2022 was 324 pg/mL. He was advised thrice weekly dialysis in view of persistent pruritis for which the patient did not oblige. On admission, computerized tomography (CT) and magnetic resonance imaging of the brain revealed an acute infarct in the left centrum semiovale. Workups involving causes of recurrent ischemic stroke including cardioembolism, hyperhomocysteinemia, anatomical and prothrombotic workups were negative. After 5 days of hospital admission, the patient developed tense pruritic bullous lesions on the medial aspect of the left leg with non-healing ulcers (Figure 1) followed by involvement of the right leg and upper limbs sequentially. Laboratory examinations revealed hemoglobin: 8.6 g/dL, white blood cells:

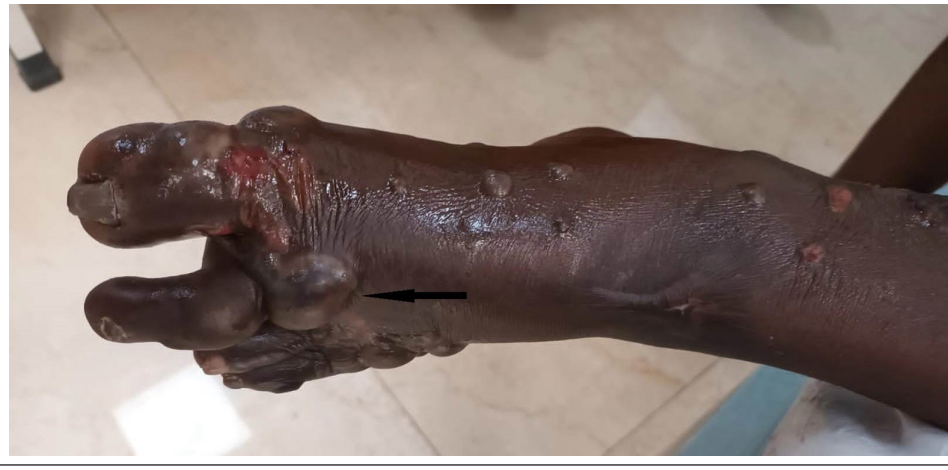

Figure 1. Medial aspect of the left leg showing tense bullous lesions (black arrow) with non-healing ulcers

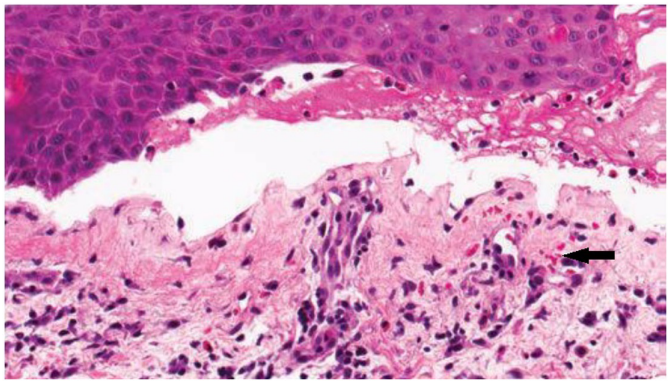

Figure 2. Histopathology of the skin showing subepidermal blisters, associated superficial dermal inflammatory infiltrate with the edge of the blister revealing eosinophils in the papillary dermis (black arrow) with focal extension of inflammatory cells into the spongiotic epidermis.

12 040/mm^3, and platelets: 174 000/mm^3. Peripheral blood smear showed normocytic anemia with neutrophilic leukocytosis without evidence of atypical cells. The dermatologist advised a skin biopsy which revealed subepidermal blisters, associated superficial dermal inflammatory infiltrate with the edge of the blister revealing eosinophils in the papillary dermis (Figure 2), and focal extension of inflammatory cells into the overlying spongiotic epidermis suggestive of bullous pemphigoid. Immunofluorescence did not reveal any significant deposits. Computerized tomography of the thorax and abdomen failed to reveal any obvious solid organ malignancy. After comprehensive discussion, it was decided to start steroids at the dose of 1 mg/kg/day with topical steroids, which resulted in partial clinical resolution of bullae in 3 weeks (Figure 3). The patient was advised to continue low-dose steroids (5 mg prednisolone) beyond 3 weeks with a bimonthly follow-up in the dermatology department.

DISCUSSION

Bullous pemphigoid is an autoimmune blistering dermatosis in hemodialysis patients with an incidence of 2.5-42.8/million in Europe.[1] General risk factors for bullous pemphigoid include

MAIN POINTS

- Bullous pemphigoid is an autoimmune bullous dermatosis in hemodialysis patients possessing risk factors such as old age, neurological disorders, chronic pruritis, and medications like nifedipine.
- Neurological and psychiatric manifestations are commonly associated with bullous pemphigoid.
- Immunofluorescence negative bullous pemphigoid may be due to low immune complex load, sampling error, or use of steroids.
- Prompt histopathological diagnosis and treatment with steroids may result in profound clinical resolution.

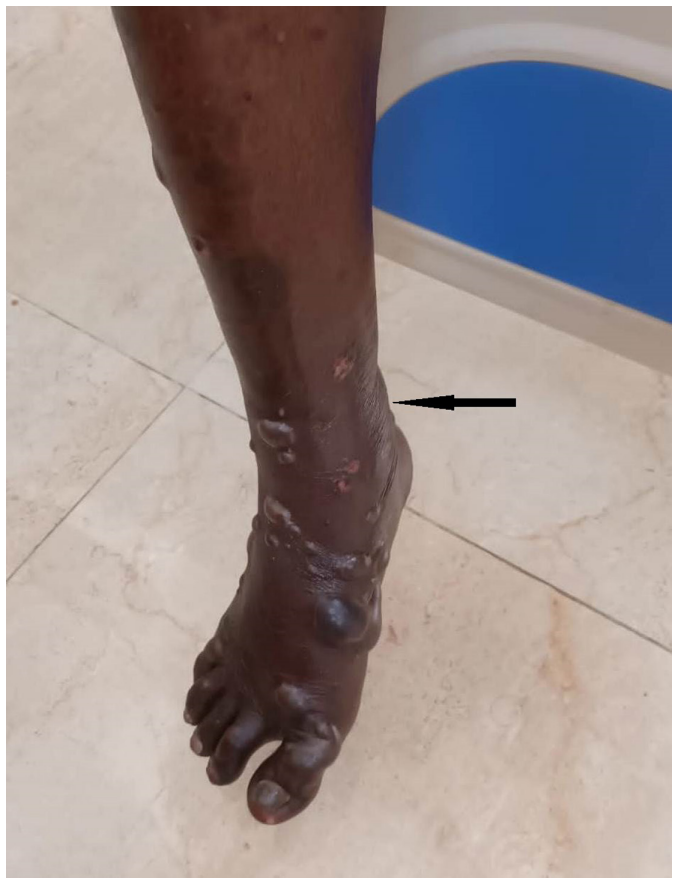

Figure 3. Right leg showing partially healed lesions (black arrow) with few scattered bullous lesions at the end of 3 weeks.

cognitive impairments, bipolar disorders, Parkinson's disease, chronic analgesic use, spironolactone use, and a bedridden state.[2] Risk factors in end stage kidney disease for bullous pemphigoid are chronic pruritis, sun exposure, neurological disorders, old age, medications like nifedipine and furosemide, mechanical trauma, and repeated skin injury.[3] Our patient had risk factors like chronic pruritis due to suboptimal dialysis, old age, recurrent cerebrovascular accidents, and nifedipine use for the development of bullous pemphigoid. Recurrent ischemic stroke and bullous pemphigoid may be part of the same autoimmune spectrum probably due to sharing of BPAG-1 antigen expressed by the neurons and Schwann cells of the central nervous system and skin.[4] The progression of atherosclerosis, thrombosis, plaque rupture, and ischemic stroke in bullous pemphigoid may be attributed to endothelial dysfunction and inflammatory markers like interleukin-6, tumor necrosis factor alpha, and soluble E selectin.[5] Bullous pemphigoid may be associated with squamous cell carcinoma of the lung, gastric cancer, and certain hematological conditions like mycosis fungoides[6] highlighting the importance of ruling out internal malignancies in this clinical scenario. Our patient's peripheral blood smear did not reveal any atypical cells, and CT screening of the thorax and abdomen grossly ruled out any solid organ

tumors. Our case is unique since the direct immunofluorescence was negative. Possible reasons for negative direct immunofluorescence include a low antigenic load, sampling error, or use of systemic steroids in treatment.[1] Bullous pemphigoid is a chronic disease process which may require treatment from 4 weeks to 6 months with steroids, azathioprine, methotrexate, or doxycycline.[1,4] Response to treatment is dependent on clinical severity and comorbidities like old age, end-stage renal disease, underlying malignancy, and neurological dysfunction.[1,3,4] Prompt recognition and immediate treatment with topical and systemic steroids will have a profound clinical resolution in bullous pemphigoid.[4]

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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