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Case Report

Primary Adrenal Insufficiency After COVID-19 Infection

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ABSTRACT

Background/Objective: The multisystemic effects of COVID-19 are becoming evident. In the adrenal gland, adrenal hemorrhage and infarction after COVID-19 infection have been reported. Our objective is to present a case of autoimmune adrenal insufficiency diagnosed after COVID-19 infection, without the evidence of a hemorrhage or an infarction.

Case Report: A 64-year-old woman with hypothyroidism and type 2 diabetes presented with a 1-week history of abdominal pain, nausea, and vomiting. She had experienced asymptomatic COVID-19 infection 5 months prior and reported an unintentional 30-lb weight loss. The home medications included enalapril, atorvastatin, and levothyroxine. A physical examination was notable for hypotension, epigastric tenderness, and mucocutaneous hyperpigmentation. Laboratory tests revealed a serum sodium level of 117 mmol/L (range, <20 mmol/L), thyroid-stimulating hormone level of 0.33 μIU/mL (range, 0.35-4.00 μIU/mL), free thyroxine level of 1.4 ng/dL (range, 0.6-1.7 ng/dL), serum osmoles of 253 mOsm/kg (range, 279-300 mOsm/kg), urine osmoles of 324 mOsm/kg (range, 300-900 mOsm/kg), and urine sodium level of 104 mmol/L. The morning cortisol level was 2.6 μg/dL (reference [ref], >18 μg/dL). This was followed by a high-dose, 250-μg adrenocorticotropic hormone (ACTH) stimulation test, which revealed that the cortisol level was 2.3, 2.9, and 2.6 μg/dL (ref, >18 μg/dL) at baseline, 30 minutes, and 60 minutes, respectively. The ACTH level was 1944 pg/mL (range, 7.2-63.3 pg/mL), the aldosterone level was <3.0 ng/dL (range, 4.0-31.0 ng/dL), and anti-21-hydroxylase antibody was present (ref, negative). A computed tomography scan of the adrenals was unremarkable. Hypotension and hyponatremia resolved after initiation of intravenous hydrocortisone, and she was discharged on hydrocortisone and fludrocortisone.

Discussion: The patient's symptoms, elevated ACTH level, low cortisol level, and presence of 21-hydroxylase antibodies were consistent with Addison disease. COVID-19 might have contributed to rapid, clinically relevant disease progression after the infection.

Conclusion: The development of autoimmune Addison disease in the patient might be related to the prior COVID-19 infection.

Introduction

SARS-CoV-2, officially known to be the cause of COVID-19, is a novel human pathogen reported to have originated from Wuhan, China, in around December 2019.[1] The major organ system affected is the respiratory system, with viral spread occurring predominantly through respiratory droplets. Disease severity varies broadly from asymptomatic disease to acute respiratory distress syndrome, multiorgan failure, and death.[2] Following its discovery, however, it became clear that COVID-19 not only causes a respiratory infection but is also responsible for many disease-related syndromes due to its ability to affect various organs and tissues, including the lungs, heart, blood vessels, brain, liver, gastrointestinal tract, kidney, and multiple organs within the endocrine system.[3,4]

The short- and long-term effects of COVID-19 infection on the endocrine system are beginning to be known and remain an area of active research. Several case reports have documented the onset of

Abbreviations: AAI, autoimmune adrenal insufficiency; AI, adrenal insufficiency; CT, computed tomography.

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Table 1
Additional Laboratory Results to Rule Out Hypothyroidism and Work Up Hyponatremia

Test name	Result	Reference range	Units
TSH	0.33	0.35-4.00	μIU/mL
Free T4	1.4	0.6-1.7	ng/dL
Serum osmolality	253	279-300	mOsm/kg
Urine osmolality	324	300-900	mOsm/kg
Urine sodium	104	<20	mEq/L
AM cortisol	2.6	>18	μg/dL

Abbreviations: T4 = thyroxine; TSH = thyroid-stimulating hormone.

adrenal insufficiency (AI) after COVID-19 infection based on the presence of an adrenal hemorrhage or infarction.[5,6] However, the full effects of the infection on cortisol dynamics remains poorly understood.

Here, we present a patient with no prior history of adrenal pathology or glucocorticoid use who was diagnosed with clinically evident AI after recovery from COVID-19 infection, the clinical infection course and imaging modalities of which were not consistent with those of adrenal hemorrhage, hypercoagulability, or adrenal infarction. Interestingly, the patient was found to have anti-21-hydroxylase antibodies, consistent with immune-mediated Addison disease in the COVID-19 sequelae. Our report suggests a potential association between the development of clinically significant autoimmune adrenal insufficiency (AAI) and COVID-19 infection.

Case Report

A 64-year-old woman with type 2 diabetes and hypothyroidism, without prior glucocorticoid use or Addison disease diagnosis, presented with a 1-week history of abdominal pain, nausea, and vomiting. The home medications included 100 μg of levothyroxine daily, 10 mg of atorvastatin daily, and 2.5 mg of enalapril twice a day. She had no family history of autoimmune disorders and no prior surgeries. She had experienced asymptomatic COVID-19 infection 5 months prior and reported an unintentional 30-lb weight loss since then. Within the last 5 months after COVID-19 infection, the patient presented twice to another hospital with nausea, vomiting, and poor oral intake. She was admitted each time for these symptoms and was subsequently found to have a low sodium level, which was thought to be due to syndrome of inappropriate antidiuretic hormone secretion. She was discharged for home after the sodium levels corrected with fluid restriction.

Upon a physical examination, the patient's blood pressure was found to be 93/66 mm Hg, and epigastric tenderness and hyperpigmentation of the oral mucosa were noted. Blood tests showed a sodium level of 117 mEq/L (range, 135-145 mEq/L), thyroid-stimulating hormone level of 0.33 μIU/mL (range, 0.35-4.00 μIU/mL), free thyroxine level of 1.4 ng/dL (range, 0.6-1.7 ng/dL), urine sodium level of 104 mmol/L (<20 mmol/L), and osmotic concentrations of 253 mOsm/kg (range, 279-300 mOsm/kg) in the serum and 324 mOsm/kg (range, 300-900 mOsm/kg) in the urine. These laboratory results were consistent with hypo-osmolar hyponatremia (Table 1).

Upon an adrenal function assessment, the patient's 8 AM cortisol level was 2.6 μg/dL (Reference [ref], >18 μg/dL). A high-dose, 250-μg adrenocorticotropic hormone (ACTH) stimulation test was performed, which revealed that the cortisol level was 2.3, 2.9, and 2.6 μg/dL (ref, >18 μg/dL) at baseline, 30 minutes, and 60 minutes, respectively. Follow-up laboratory results showed an ACTH level of 1944 pg/mL (range, 7.2-63.3 pg/mL) and an aldosterone level of <3 ng/mL (range, 4.0-31.0 pg/mL) (Table 2).

Table 2
Adrenal-Specific Testing Reveals Primary Adrenal Insufficiency (Addison Disease)

Test name	Result	Reference range	Units
ACTH	1944	7.2-63.3	pg/mL
Aldosterone	<3	4.0-31.0	ng/dL
Anti-21-hydroxylase antibody	Positive	Negative	

Abbreviations: ACTH = adrenocorticotropic hormone.

Abdominopelvic computed tomography (CT) imaging showed unremarkable adrenal glands (Fig.). The anti-21-hydroxylase antibody was present, without a specific level reported (ref, negative, Associated Regional and University Pathologists, Inc Laboratories) (Table 2). Hypotension and hyponatremia resolved after initiation of 25 mg of intravenous hydrocortisone every 8 hours. Her clinical status significantly improved, the glucocorticoid was weaned, and the patient was discharged in a stable condition on 30 mg of hydrocortisone daily and 0.05 mg of fludrocortisone daily.

Discussion

Our patient presented with hyponatremia and the biochemical evidence of AI after COVID-19 infection, which was confirmed based on an abnormal cortisol response to the high-dose ACTH stimulation test. The markedly elevated ACTH level, inappropriately low aldosterone level, and presence of anti-21-hydroxylase antibodies support the diagnosis of AAI.

Addison disease is a primary adrenocortical deficiency resulting from damage to the adrenal cortex, which does not become clinically apparent until 80% to 90% of both adrenal cortices are destroyed.[7–9] The causes of Addison disease include infections, infiltration, hemorrhage, and, most commonly in Western countries, autoimmunity.[7] In our patient, clinical hypoadrenalism did not manifest until after her COVID-19 infection, which raises the possibility of a potential association between these.

AI associated with COVID-19 infection has been previously reported in the literature in context of adrenal hemorrhage or infarction. In 1 example, a 70-year-old woman presented with fever, cough, fatigue, abdominal pain, and nausea.[6] Serology for COVID-19 was positive. Hypotension and serum chemistry with hyponatremia was concerning for AI. In the setting of acute abdominal complaints, abdominopelvic CT scan was performed, revealing enlarged, diffusely hypoattenuating adrenal glands with poor enhancement, suggestive of a nonhemorrhagic adrenal infarction. In a second case, a 69-year-old man presented with fever and abdominal pain.[5] Similarly, he was positive for COVID-19 and was found to be hyponatremic. Vital signs revealed hypotension, and a physical examination showed mucocutaneous hyperpigmentation. Abdominal CT scan demonstrated a bilateral adrenal hemorrhage. COVID-19 has been known to cause a hypercoagulable state, which makes highly vascularized organs, such as the adrenal glands, susceptible to infarction and hemorrhage.[10] The imaging result of our patient's adrenal glands was unremarkable (Fig.), suggesting that her AI was not related to an infarction or a hemorrhage.

Anti-21-hydroxylase antibodies are present in >90% of AAI cases, and it serves as a sensitive and specific marker for AI, with its detection strongly associated with autoimmune destruction of the adrenal cortex.[8] Despite being a reliable marker for the disease, these antibodies are not thought to directly mediate the disease or the pathology of AAI, and as such, the biochemical mechanism of AAI is yet to be fully elucidated. Dawoodji et al[8] identified 21-hydroxylase-specific T cells in patients with AAI and determined that these cells might be related to disease progression.

As with AAI, the pathogenesis of many autoimmune conditions remains unclear, but an interplay between genetic predisposition

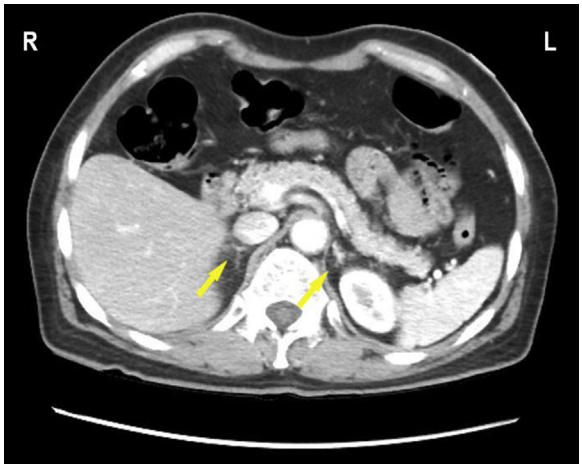

Fig. Abdominopelvic computed tomography without contrast upon initial presentation. Imaging of the patient's abdomen demonstrated grossly normal-appearing adrenal glands (yellow arrows).

and environmental factors, such as viral and bacterial infection, are thought to play a major role.[9,11,12] Certain viruses could partake in development of AAI either by infecting steroid hormone-producing cells of the adrenal cortex or by affecting the balance of the immune system.[9] Autoimmunity can be induced by infectious agents via varying mechanisms, such as epitope spreading, standard activation, and autoinflammatory activation of innate immunity, to name a few.[12] Specifically, SARS-CoV-2 has been shown to produce viral amino acid sequences homologous to that of ACTH; however, antibodies produced to counteract these sequences destroy the host's ACTH and blunt cortisol response, which would cause secondary rather than primary AI. Additionally, infections can also target the site of autoimmune inflammation and amplify the immune disease instead of being directly responsible for the induction of autoimmunity.[12]

The precise methods by which COVID-19 negatively affects adrenal function have not yet been fully elucidated. The development of AAI is an insidious process with a long subclinical phase, with symptoms of hypercortisolism appearing years after adrenal gland destruction begins.[8,9] Therefore, it is challenging to identify an acute or subacute infectious etiology that could have a role in the pathogenesis of AAI.[13] Preclinical adult patients with anti-21-hydroxylase antibodies have an approximately 20% risk of developing overt Addison disease.[8] Our patient's past medical history of hypothyroidism predisposed her to the development of additional autoimmune conditions and polyglandular disorders.[14] However, patients with an initial diagnosis of autoimmune thyroid disease without a family history of polyglandular disorders have a relatively low probability of developing additional autoimmune disorders compared with patients whose initial diagnosis is a less common disorder.[13,15] Up to 40% to 50% of patients with an initial diagnosis of Addison disease progress to develop a second endocrinopathy.[13,15] Despite the predisposition, ≥20 years can elapse between the onset of 2 different endocrinopathies.[13]

A variety of factors can trigger an autoimmune disease, and 1 disorder can have multiple triggering factors.[15] Whether our patient's COVID-19 infection was a causal event for the development of AAI or whether the viral infection had a role in furthering the development of clinically significant AI remains unclear. Infections can also target the site of autoimmune inflammation and amplify the immune disease instead of being directly responsible for the induction of autoimmunity.[12] It is a strong possibility that our patient had anti-21-hydroxylase antibodies and ongoing adrenal cortex destruction prior to contracting COVID-19 infection, but the rapid progression to clinically significant AI after the infection raises the question whether the infection served to target the patient's adrenal glands as a site of autoimmune inflammation, serving as a catalyst to the clinical presentation of her AAI.

Conclusion

In susceptible patients, such as those with previously known endocrinopathies, COVID-19 infection might promote the development or progression of clinically significant AI through an adrenal hemorrhage or infarction or via autoimmunity. Given the severity of undiagnosed hypocortisolism and our current understanding of the various mechanisms by which COVID-19 can cause AI, it is important to include AI in the differential diagnosis in patients with a corresponding clinical scenario during or after a COVID-19 infection.

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Disclosure

The authors have no multiplicity of interest to disclose.

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