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Adrenal Infarction - An Early and Late Complication of COVID-19: A Case Report

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Abstract: Progressive respiratory failure and the hyperinflammatory response are among the primary causes of death in COVID-19. Although various organ system complications have been identified post-COVID, among which one of the most important endocrine disorders is hypothalamus-pituitary-adrenal gland connection disruption, there is still little information about virus-induced adrenal gland tropism. Among the multisystemic effects of the COVID-19 pandemic, researchers are focusing on adrenal hemorrhages and infarcts. The aim of the article is to present and discuss clinical case of autoimmune adrenal gland failure developed post-COVID. The impact of COVID-19 was studied in 3 phases: The phase of acute active infection, Immediate post-infection phase and Long-term recovery phase. Adrenal insufficiency associated with COVID-19 has been reported in the literature in the context of hemorrhage and infarction. As a result of the studies, it was determined that the administration of large amounts of hydrocortisone to patients during the acute active phase of COVID-19 makes it impossible to fully evaluate the function of the gland. After stopping treatment with hydrocortisone, adrenal insufficiency was detected 1 month following the infarction. It has been established that during the long-term recovery phase, the possibility of insufficient cortisol is observed in most patients. In this case, the cause is central adrenal insufficiency. Considering all this, we can say that adrenal gland failure is a late phase complication of COVID-19. After transmission of COVID-19, complications are associated with insufficient production of cortisol by the adrenal gland. It is important to evaluate issues in post-COVID patients to avoid life-threatening adrenal crises.

Keywords: *COVID-19; Adrenal Infarct; Complications of COVID-19; Adrenal Insufficiency.*

Introduction

Early and late complications of COVID-19, specifically caused by adrenal infarction, are quite relevant issues, because the disease itself and, accordingly, its complications are still a great subject of study and observation(Boughton, 2022; Clarke, 2022; Luke, 2022). The new coronavirus is a new strain of corona viruses. It binds to the same group of viruses as „Severe Respiratory Syndrome“(SARS) and some forms of colds. After the acute phase of SARS-COV-2 infection, approximately 20% of patients have one or more complications.

Post-COVID complications are: chronic weakness, shortness of breath, headache, brain fog, joint pain, cough, abdominal pain(Jensterle, 2022; Mirza, 2022; Rodríguez, 2022). When these symptoms persist for 4 weeks or more after the onset of infection, and are not associated with other known chronic diseases, they are described as Long COVID. The effect of the virus on such an important organ of the endocrine system as the adrenal gland is particularly interesting. A clinical case recorded in one of the clinics in Tbilisi, Georgia was used to study the issue in depth, although it should be noted that this issue is still a subject of active study today(Kanczkowski, 2022; Morita, 2022; Urhan, 2022).

Methodology

This case report examines the development of adrenal infarction as a complication of COVID-19 in a 19-year-old female patient. The study was conducted in a clinical setting at a healthcare facility in Tbilisi, Georgia, and was aimed at understanding the potential endocrine disturbances induced by COVID-19, particularly adrenal insufficiency. The following phases of COVID-19 infection were evaluated: the acute active infection phase, the immediate post-infection phase, and the long-term recovery phase.

1. **Patient Selection**

   The patient presented with complaints of acute abdominal pain, general discomfort, heart palpitations, and bloating. Prior to her visit, an abdominal ultrasound identified a small amount of fluid near the right kidney, leading to her referral for further investigation. Upon clinical assessment, the patient's physical examination revealed moderate abdominal swelling, localized tenderness, and signs of increased muscle tone in the right abdominal quadrant.

2. **Clinical Assessment**

   The patient underwent a thorough clinical evaluation, including a history of recent symptoms and signs suggestive of adrenal insufficiency. The initial rapid test for COVID-19 was negative; however, a subsequent PCR test confirmed the diagnosis of COVID-19. The patient was then referred for further imaging studies, which included a Computed Tomography (CT) scan of the abdomen. The CT scan identified right adrenal infarction as a significant finding.

3. **Diagnostic Imaging**

   To assess the extent of the adrenal injury, CT imaging was performed, which confirmed the presence of an adrenal infarction. The imaging technique used allowed for a detailed examination of the adrenal glands, which revealed characteristic signs of infarction.

4. **Laboratory Testing**

During the clinical investigation, laboratory tests were performed to assess hormone levels, particularly cortisol and other adrenal function markers. Although the rapid test for COVID-19 was negative initially, the PCR test confirmed the presence of SARS-CoV-2 infection. Hormonal assays were planned for future evaluation, but immediate tests during the acute phase were influenced by corticosteroid treatment, which had been administrated to the patient for managing COVID-19 symptoms.

5. **Phase of Evaluation**

The study focused on three distinct phases:

- **Acute Infection Phase**: The patient received corticosteroid treatment during the active COVID-19 infection to manage inflammation and respiratory distress.
- **Immediate Post-Infection Phase**: After the acute infection, the patient's adrenal function was monitored, particularly for signs of adrenal insufficiency following the cessation of corticosteroid treatment.
- **Long-Term Recovery Phase**: The patient's adrenal function was reassessed one month following the cessation of corticosteroids to investigate potential delayed-onset adrenal insufficiency, and the presence of central adrenal insufficiency was monitored through repeated tests.

6. **Outcome Measures**

The primary outcome measures included the presence of adrenal insufficiency, assessed through clinical signs, hormonal assays, and radiological imaging. The secondary outcomes involved monitoring for any long-term complications associated with adrenal gland failure, including the need for replacement therapy with hydrocortisone.

This methodology outlines the clinical process of patient evaluation, diagnostic techniques, and monitoring over different phases of COVID-19 infection. It also ensures the systematic approach to detecting complications like adrenal infarction and insufficiency, highlighting the use of imaging and laboratory testing as key components in diagnosing this serious post-COVID complication.

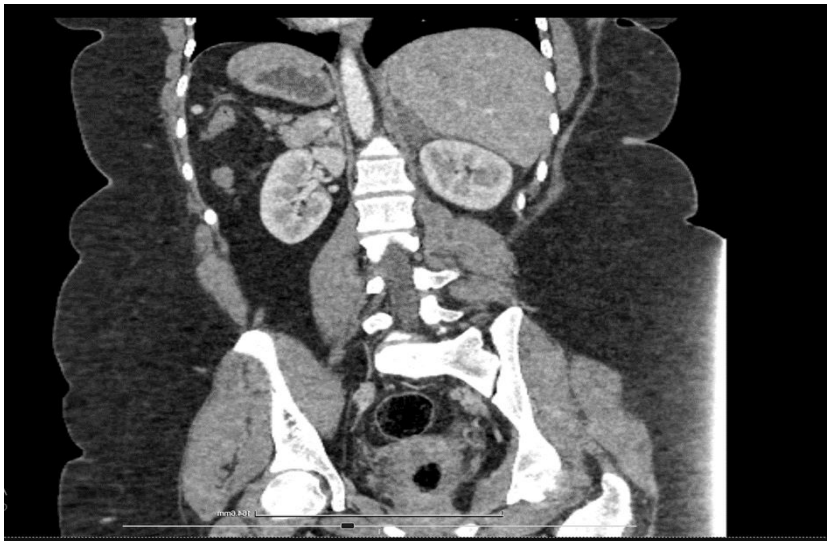
Result and Discussion

Case description

A 19-year-old female patient visited the clinic on her own. The patient complained of sharp pain in the abdomen, mainly in the right half, heart palpitations, dry mouth, bloating, general discomfort. These complaints developed in the morning and the pain in the right half of the abdomen became growing and intense. In connection with the complaints, before coming to the clinic, an ultrasound examination of the abdominal cavity was performed, as a result of which a small amount of fluid was detected near the right kidney. Due to the increase in dynamic complaints, the patient was brought to the clinic by relatives. An

objective examination determined: the abdomen was moderately swollen, participating in breathing, soft on palpation, diffusely painful, more so in the right half of the abdomen, where relatively increased muscle tone was expressed.

Bloomberg's symptom is locally weakly expressed in the right half of the abdomen. Peristalsis was heard slowly, diuresis increased, Pasternak's sign was weakly expressed, positive on the right side. Studies were carried out- Computed Tomography (CT) - showed right adrenal gland infarction. Upon entering the clinic, the result of a rapid test for COVID was negative. Since adrenal infarction and hemorrhage are one of the complications of COVID, it was decided that the patient would undergo a PCR test, the result of which was positive.



CT Imaging - Right Adrenal Infarction

Discussion

The adrenal gland plays an important role in the body's immune response. The hormones produced by it regulate blood pressure and are responsible for the body's reaction to stressful situations. Bacteria and viruses are characterized by tropism towards the adrenal gland. Adrenal gland failure is often observed in meningococcemia sepsis, inflammation of the adrenal gland of tuberculous origin, and opportunistic viral infections.At the beginning of the COVID-19 pandemic, there were cases of development of adrenal insufficiency in the acute phase of the disease.

COVID-19 is associated with a high risk of bilateral adrenal hemorrhage and immune inflammatory changes. In one retrospective study involving 219 patients with severe COVID-19, 23% of them were diagnosed with adrenal infarction, including 8% with biochemical hypocortisolism in a radiological study. (Alzahrani AS, 2020). Several mechanisms have been proposed, including a cytokine storm, which causes a decrease in the release of anticorticotropic hormone, as well as a decrease in the function of this hormone(Alzahrani, 2021; Gupta, 2021; Hermine, 2021). The function of the hormone Angiotensin II also decreases. Adrenal cells, as targets for COVID, can express an Angiotensin-Converting Enzyme (ACE2) that can bind virus protein to the cell surface. Some studies claim that the adrenal gland is not only a target for the virus, and the virus can also multiply inside the gland cells. Autopsy studies showed RNA and protein of the virus in the adrenal glands of 45% of those who died due to COVID. The coronavirus has

also been found in the endothelial cells of the gland, no evidence of its reproduction has been seen in these cells, indicating that COVID-19 has been passively hematogenous transmitted. (Freire Santana,2020).

COVID is associated with increased inflammatory changes in human adrenocortical cells. Histological examination of the adrenal gland often (in 90%) reveals lymphocytic infiltration and pronounced inflammation in the blood vessels of the gland, parenchyma of the gland and surrounding adipose tissue(Frara, 2021; Mao, 2021; Puig-Domingo, 2021). An autopsy looked at ischemic necrosis, cortical fatty degeneration, hemorrhages, and non-specific focal adrenaline. Nevertheless, massive degeneration of adrenocortical cells has not been seen, which can cause complete functional adrenal insufficiency. COVID-19 is known as vascular disease. The virus is associated with adrenal hemorrhage and infarction. Histopathological autopsies showed deposits of fibrin and microthrombus in the capillaries of the gland. The adrenal gland can receive 10 times more blood volume than its size. Unilateral and bilateral adrenal infarctions often occur during computed tomography studies of patients, regardless of whether the disease is severe or moderate. Vascular damage caused by COVID can cause potentially life-threatening adrenal insufficiency.

COVID can also cause reversal dysfunction in patients known as corticosteroid failure associated with critical illnesses. Many factors can cause this condition, including: hypothalamic-pituitary-adrenal chain dysregulation, reduced cortisol metabolism, or glucocorticoid receptor alpha cell resistance. The frequency of this syndrome, with moderate and severe course of COVID, appears in 4.4 -32.0% of patients. (Kanczkowski W, 2022). Since most studies in the acute period of COVID indicated a normal level of cortisol, adrenal insufficiency still cannot be ruled out, since its manifestation can occur late or be disguised by low cortisol metabolism. Adrenal gland failure usually develops within a few weeks of the acute phase of the disease, which may be due to dysregulation of the already existing hypothalamic-pituitary-adrenal chain, reactivation of latent viral infections or an autoimmune response involving adrenocortical cells. [4] [5]

Although there is still insufficient solid clinical evidence, in some cases a high titer of anticorticotropic hormone antibodies has been seen, which indicates a potentially pathophysiological mechanism - adrenocorticotropic insufficiency caused by COVID-19. Secondary adrenal insufficiency caused by high doses of glucocorticoids from COVID -19 should also be considered. In one study that examined more than 2,000 patients, 30% of whom received glucocorticosteroids for 6 weeks or more, was found that long-term steroid use causes secondary adrenal insufficiency. Such patients should take corticotropin-

releasing hormone stimulants to prevent secondary adrenal insufficiency. (Popescu M,2022) [6]

Conclusion

Ultimately, adrenal insufficiency can be caused by the following mechanisms: damage to blood vessels, viral replication, inflammatory factors, and prolonged corticosteroid therapy.Although adrenal cells have a tendency to become infected with the virus, it is not necessary that COVID causes clinically relevant gland failure.Some medical professional organizations recommend that patients with adrenal insufficiency and those who are on replacement therapy should be strictly monitored after the COVID-19 vaccination to avoid developing stress-induced adrenal insufficiency.

Since computed tomography of the abdominal cavity with contrast is not considered a routine study in COVID patients, radiological diagnosis of adrenal gland pathologies is less common. At the same time, when corticosteroid therapy is involved in the treatment of the main disease, the functional state of the adrenal gland cannot be assessed at all. Based on each of the above, there is a high probability that we will miss such a complication of potentially life-threatening COVID as adrenal insufficiency, which can be manifested both in the acute and late phase of the disease, therefore it is important to monitor such patients.

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