Research Article

Journal of Clinical Endocrinology and Metabolism

Insufficiency of Primary Adrenals Owing to COVID-19 Bilateral Adrenal Infarction.

Asabel Nenezes , Kabrina Rigueiredo and Lebora Eerrabuio

***Corresponding author**

Asabel Nenezes,
Unidade de Adrenal, Laboratório de Hormônios e Genética Molecular LIM/42, Divisão de Endocrinologia e Metabologia, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Received Date : May 20, 2024
Accepted Date : May 22, 2024
Published Date : June 22, 2024

ABSTRACT

Context : Although COVID-19 is a prothrombotic and proinflammatory illness, its effects on adrenal function have not been sufficiently studied.
Report on a case : Following a COVID-19 infection, a 46-year-old lady showed signs of hyperpigmentation, hypotension, and abdominal pain. Serum cortisol was less than 1.0 µg/dL, aldosterone was less than 3 ng/dL, and adrenocorticotropin (ACTH) was 807 pg/mL in the patient with hyponatremia.
Bilateral adrenal infarction was supported by computed tomography (CT) observations of adrenal enlargement with no parenchymal and little peripheral capsular enhancement following contrast. The patient had no prior thrombotic episodes, although she did have positive antiphospholipid antibodies and autoimmune hepatitis. Intravenous hydrocortisone was used as the first treatment for the patient, and then oral hydrocortisone and fludrocortisone.
Discussion : In COVID-19, we found nine articles—including case reports—that described adrenal insufficiency that developed recently and/or adrenal hemorrhage or infarction on CT. Five cases had hormonal diagnoses of adrenal insufficiency, although only three had measured ACTH levels (high in one, normal/low in the other two). Five studies showed evidence of bilateral adrenal hemorrhagic or nonhemorrhagic infarction (two with adrenal insufficiency, two with normal cortisol levels, and one with no data). It's interesting to note that antiphospholipid syndrome was previously diagnosed in the lone instance with well-characterized new-onset acute primary adrenal insufficiency following COVID-19. In our instance, the diagnosis of antiphospholipid syndrome was made subsequent to the COVID-19-induced adrenal infarction. In conclusion, our results corroborate the hypothesis that COVID-19-induced antiphospholipid syndrome and bilateral adrenal infarction are related. Consequently, during COVID-19, individuals with positive antiphospholipid antibody tests need to be cautiously watched for any indications of severe adrenal insufficiency.

Keywords : Bilateral adrenal infarction, primary adrenal insufficiency, antiphospholipid syndrome, COVID-19.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the cause of Coronavirus Disease 2019 (COVID-19), a prothrombotic and proinflammatory illness (1-3).
A multicenter retrospective research found that patients with COVID-19 had an overall thrombotic complication rate of up to 10% (4). A notable increase in D-dimer and fibrin/fibrinogen degradation products is indicative of COVID-19 coagulopathy (5). When patients with COVID-19 have elevated D-dimer readings and/or are admitted to the intensive care unit, antithrombotic treatment has been utilized often (6).

Even though prothrombotic symptoms have been linked to COVID-19, it is unclear how the adrenal gland is involved in COVID-19 coagulopathy. Microscopic abnormalities including necrosis, inflammation, vascular thrombosis, and hemorrhage were seen in 46% of the adrenal glands in an autopsy investigation (7). In patients with severe COVID-19, perivascular infiltration of CD3+ and CD8+ T-lymphocytes has also been seen in the adrenal glands (8). Nevertheless, there hasn't been enough research done to determine how these pathological changes affect adrenal function. Adults with primary adrenal insufficiency are primarily affected by acquired etiologies, such as viral or autoimmune diseases (9). Here, we describe a patient who developed a bilateral adrenal infarction following a COVID-19 infection, resulting in an adrenal crisis. We also conducted a literature study on COVID-19-related new-onset adrenal insufficiency.

PRESENTATION OF A CASE

A 46-year-old woman arrived complaining of a two-day sore throat. She was admitted to the hospital for assessment

and evaluation after experiencing malaise, nausea, and prostration over the course of the following 20 days. On the first day of admission, she complained of sudden, severe stomach discomfort that was accompanied by vomiting, which made her symptoms worse. Both potassium and sodium levels in the serum were normal. Lung computed tomography (CT) imaging in the first study showed bilateral, peripheral ground glass opacities and consolidations in the lower lung lobes with less than 25% parenchymal involvement. An abdomen CT scan showed normal adrenal function and no abnormalities (Fig. 1).The patient did not report any dyspnea symptoms, and his oximeter readings were normal. High titers of SARS-CoV-2 immunoglobulin (Ig)M and IgG antibodies were found by COVID-19 serology. Since the COVID-19 reverse transcription polymerase chain reaction was obtained 20 days after the onset of symptoms, it was negative at this time. Due to stomach discomfort, the patient was sent home with analgesics.

She experienced increased symptoms of lethargy, vomiting, nausea, and hyperpigmentation, leading to her readmission after three weeks. She had reflex tachycardia, postural hypotension, and hyperpigmentation on her tongue, hands, elbows, and cheeks (Fig. 2). She had no prior thrombotic events and autoimmune hepatitis in her medical background. She had reached sustained remission from her autoimmune hepatitis, thus she was not on any immunosuppressant medicine. An abdominal CT scan six months prior to the COVID-19 infection showed an enlarged liver along with parenchymal disease indicators and normal adrenal function (Fig. 3A). After undergoing abdominal magnetic resonance imaging (MRI), the patient's adrenal glands were found to be heterogeneously hyperintensly swollen and diffusely enlarged. The absence of fundamentally high signal intensity within the anomaly (dashed arrows) on axial fat-suppressed T1-weighted MRI revealed no bleeding (Fig. 3B-3E).Following COVID-19 infection, a reformatted postcontrast CT scan showed left adrenal vein thrombosis (Fig. 4). Because the enlarged adrenal gland and right adrenal vein could not be distinguished on imaging, the right adrenal vein thrombosis was not visible.The patient was referred to our facility for additional testing following an abdominal magnetic resonance imaging. The patient received intravenous hydrocortisone (100 mg bolus followed by 50 mg administered every 6 hours) and hydration therapy as soon as blood was drawn for biochemical and hormonal examination. Adrenocorticotropin (ACTH) was 817 pg/mL (normal: 7.2-63.3) and serum cortisol was 1.3 µg/dL (normal: 3.7-19.4 µg/dL), supporting the diagnosis of primary adrenal insufficiency. The plasma renin concentration was not detected, although the amount of aldosterone was less than 3 ng/dL. The patient's serum potassium was at the upper normal limit (4.8 mEq/L; normal: 3.5-5.0 mEq/L), hyponatremia (133 mEq/L; normal: 135-145 mEq/L), and metabolic acidosis (19.1 mmol/L of bicarbonate, compared to normal values of 23–27 mmol/L; pH 7.29, 7.35-7.45). The diagnosis of primary adrenal insufficiency was made with absolute certainty due to the elevation of ACTH (>2-fold above the upper limit of the reference period) and basal cortisol (<1 µg/dL), both of which precluded the need for an ACTH stimulation test (9). Overall symptoms were quickly resolved and returned to normal with intravenous hydrocortisone and hydration therapy blood pressure, and corrected metabolic acidosis and hyponatremia. The patient had a contrast-enhanced CT scan, which revealed limited peripheral capsular enhancement, or "capsular sign," and no parenchymal enhancement (Fig. 3F). Bilateral adrenal infarction is consistent with these results. After 48 hours, oral hydrocortisone (20 mg administered in the morning and 10 mg at 2 pm) and fludrocortisone took the place of intravenous hydrocortisone.1 mg in the morning. The patient continued hormone replacement medication and maintained a low cortisol level after a month of follow-up. The test for adrenal 21-hydroxylase antibody was unsuccessful.

It's interesting to note that since 2011, the activated partial thromboplastin time (aPTT) has increased (87.2 seconds compared to normal: 24.3–32.4 seconds). Her plasma remained changed even after it was mixed with regular plasma, indicating the possibility of interference. The presence of lupus anticoagulant (LA) was assessed using three different tests: diluted Russell viper venom time, Kaolin clotting time, and LA partial thromboplastin time (LA-PTT). In the LA-PTT test, adding diluted phospholipids dramatically lowered PTT from 102 to 22 seconds. Two further confirmatory tests yielded favorable results as well.Two further confirmatory tests yielded favorable results as well.

A positive anticardiolipin antibody was also found. The patient has had a prolonged aPTT since 2011, however she has never experienced a thrombotic episode or obstetric morbidity before. The patient had no signs of thrombosis on brain CT, abdominal MRI, or leg Doppler ultrasound performed in the previous ten years. At least one clinical criterion (thrombotic event or gestational morbidity) and at least one laboratory criterion (confirmed positive LA antibody) are needed for the diagnosis of antiphospholipid syndrome (10). Consequently, the patient's bilateral adrenal infarction following COVID-19 was the only time the patient met the diagnostic criteria for antiphospholipid syndrome. Anticoagulation treatment was started as soon as bilateral adrenal infarction was identified.

DISCUSSION

Here, we describe a patient with positive antiphospholipid antibodies who had bilateral adrenal nonhemorrhagic infarction following COVID-19, resulting in new-onset

primary adrenal insufficiency. High titers of SARS-CoV-2 IgM antibodies and bilateral ground glass opacities on lung CT were used to diagnose COVID-19. It's interesting to note that antiphospholipid syndrome was previously diagnosed in the lone patient with a well-characterized new-onset primary adrenal insufficiency following COVID-19 (11). Unlike the previously documented instance, the current individual exhibited positive anticardiolipin antibody prior to COVID-19; nonetheless, the SARS-CoV-2 infection was the cause of the initial thrombotic event, which was a bilateral adrenal infarction.

Nine studies (eight case reports) describing adrenal insufficiency with a recent start and/or adrenal hemorrhage/infarction on CT in COVID-19 patients were found (Table 1). Five individuals with a hormonal diagnosis of adrenal insufficiency were included in the eight case reports (11–15). Only three of the five patients had measured ACTH levels (one had >100 pg/mL, while the other two had normal or low levels, suggesting secondary adrenal insufficiency). As a result, only one instance of new-onset primary adrenal insufficiency may be properly described because after COVID-19, to bilateral adrenal hemorrhagic infarction (11). After a month of follow-up, only 2 patients underwent hormonal re-evaluation and continued to have low cortisol levels (11, 13).

Five case reports—two with adrenal insufficiency, two with normal cortisol levels, and one with no data—identified bilateral adrenal hemorrhagic or nonhemorrhagic infarction (11, 13, 16– 18). Hormonal testing was not done in one of these cases, which was linked to disseminated intravascular coagulation following the AstraZeneca vaccination (16). Leyendecker et al. (19) have identified incidental CT evidence of adrenal infarction in 51 out of 219 (23%) individuals with severe COVID-19 infection. Adrenal infarction is defined as enlargement of one or both adrenal glands with peripheral fat stranding in the suprarenal region (19). Nevertheless, in these cases, adrenal function (cortisol and ACTH levels) was not reported (19).

Rare disorders with a variety of causes, such as infectious diseases like traditional meningococcal infection and less frequent strains of Haemophilus influenzae and Staphylococcus aureus that cause Waterhouse-Friderichsen syndrome, are bilateral adrenal hemorrhage and thrombosis (20, 21). Adrenal hemorrhage or thrombosis can also be brought on by non-infectious disorders, trauma, burns, anticoagulant therapy, tumor metastasis, and cardiovascular disasters (9, 22).

Venous or arterial thrombosis, a complication of antiphospholipid syndrome, may be made worse by the prothrombotic state associated with COVID-19. Sadly, in the other cases of adrenal infarction, antiphospholipid antibodies were not routinely tested. Few cases of severe COVID-19 and coagulopathy have been linked to antiphospholipid antibodies, which raises the possibility that these antibodies play a role in the development of thrombosis in COVID-19 patients (23). Regardless of COVID-19 status, a recent longitudinal research comparing patients with respiratory failure who tested positive and negative for the virus found that the presence of antiphospholipid antibodies was linked to a more severe form of the disease (24). However, our case did not exhibit substantial lung involvement and had positive antiphospholipid antibodies before the COVID-19 infection.

Bilateral adrenal hemorrhagic infarction has been reported as the initial thrombotic event in patients with antiphospholipid syndrome prior to the COVID-19 pandemic (25). The adrenal glands are more prone to infarction and subsequent bleeding due to their vascular structure, which is defined by three suprarenal arteries and a single adrenal vein for limited venous drainage (26).Ultimately, our research confirms the link between COVID-19-induced bilateral adrenal infarction and antiphospholipid syndrome. Thus, during COVID-19 infection, patients with antiphospholipid antibodies should be actively watched for indications of acute primary adrenal insufficiency.

REFERENCES

1. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-374.

2. Whyte CS, Morrow GB, Mitchell JL, Chowdary P, Mutch NJ. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. J Thromb Haemost. 2020;18(7):1548-1555.

3. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost. 2020;8(6):1517-1519.

4. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARSCoV-2 infection. Blood. 2020;136(4):489-500.

5. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135(23):2033-2040.

6. Investigators I, Sadeghipour P, Talasaz AH, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal

membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA. 2021;325(16):1620-1630.

7. Freire Santana M, Borba MGS, Baia-da-Silva DC, et al. Case report: adrenal pathology findings in severe COVID-19: an autopsy study. Am J Trop Med Hyg. 2020;103(4):1604-1607.

8. Zinserling VA, Semenova NY, Markov AG, et al. Inflammatory cell infiltration of adrenals in COVID-19. Horm Metab Res.2020;52(9):639-641.

9. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364-389.

10. Pengo V, Tripodi A, Reber G, et al.; Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/ Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7(10):1737-1740.

11. Frankel M, Feldman I, Levine M. Bilateral adrenal hemorrhage in Coronavirus Disease 2019 patient: a case report. J Clin Endocrinol Metab. 2020;105(12):dgaa487.

12. Hashim M, Athar S, Gaba WH. New onset adrenal insufficiency in a patient with COVID-19. BMJ Case Rep. 2021;14(1):e237690.

13. Alvarez-Troncoso J, Zapatero Larrauri M, Montero Vega MD, et al. Case report: COVID-19 with bilateral adrenal hemorrhage. Am J Trop Med Hyg. 2020;103(3):1156-1157.

14. Chua MWJ, Chua MPW. Delayed onset of central hypocortisolism in a patient recovering from COVID-19. AACE Clin Case Rep.2021;7(1):2-5.

15. De La Flor Merino JC, Mola Reyes L, Linares Gravalos T, Roel Conde A, Rodeles Del Pozo M. An unusual case of severe acute hyponatremia in patient with COVID-19 infection. Nefrologia. 2020;40(3):356-358.

16. D'Agostino V, Caranci F, Negro A, et al. A rare case of cerebral venous thrombosis and disseminated intravascular coagulation temporally associated to the COVID-19 vaccine administration. J Pers Med. 2021;11(4):285.

17. Kumar R, Guruparan T, Siddiqi S, et al. A case of adrenal infarction in a patient with COVID 19 infection. BJR Case Rep.2020;6(3):20200075.

18. Elkhouly MMN, Elazzab AA, Moghul SS. Bilateral adrenal hemorrhage in a man with severe COVID-19 pneumonia. Radiol Case Rep. 2021;16(6):1438-1442.

19. Leyendecker P, Ritter S, Riou M, et al. Acute adrenal infarction as an incidental CT finding and a potential prognosis factor in severe SARS-CoV-2 infection: a retrospective cohort analysis on 219 patients. Eur Radiol. 2021;31(2):895-900.

20. Kovacs KA, Lam YM, Pater JL. Bilateral massive adrenal hemorrhage. Assessment of putative risk factors by the case-control method. Medicine. 2001;80(1):45-53.

21. Adem PV, Montgomery CP, Husain AN, et al. Staphylococcus aureus sepsis and the Waterhouse-Friderichsen syndrome in children. N Engl J Med. 2005;353(12):1245-1251.

22. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol.2015;3(3):216-226.

23. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020;382(17):e38.

24. Trahtemberg U, Rottapel R, Dos Santos CC, Slutsky AS, Baker A, Fritzler MJ. Anticardiolipin and other antiphospholipid antibodies in critically ill COVID-19 positive and negative patients. Ann Rheum Dis. 2021;80(9):1236-1240.

25. Presotto F, Fornasini F, Betterle C, Federspil G, Rossato M. Acute adrenal failure as the heralding symptom of primary antiphospholipid syndrome: report of a case and review of the literature. Eur J Endocrinol. 2005;153(4):507-514.

26. Fox B. Venous infarction of the adrenal glands. J Pathol.1976;119(2):65-89.