Clinical Research Article

Bilateral Adrenal Hemorrhage in Coronavirus Disease 2019 Patient: A Case Report

Meir Frankel, 1 Itamar Feldman, 2,* Michal Levine, 3 Yigal Frank, 4 Naama R. Bogot, 4,5 Ofer Benjaiminov, 4,5 Ramzi Kurd, 3 Gabriel S. Breuer, 2,3,5 and Gabriel Munter 1,3,5

1Endocrinology Unit, Shaare Zedek Medical Center, Jerusalem, Israel; 2Rheumatology Unit, Shaare Zedek Medical Center, Jerusalem, Israel; 3Department of Internal Medicine, Shaare Zedek Medical Center, Jerusalem, Israel; 4Department of Radiology, Shaare Zedek Medical Center, Jerusalem, Israel; and 5Hadassah Hebrew University School of Medicine, Jerusalem, Israel

ORCiD number: 0000-0001-5094-7719 (M. Frankel).

*Equal contribution.

Abbreviations: APLS, antiphospholipid syndrome; BAH, bilateral adrenal hemorrhage; COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

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Abstract

Context: Bilateral adrenal hemorrhage is a rare condition with potentially life-threatening consequences such as acute adrenal insufficiency. Early adrenal axis testing, as well as directed imaging, is crucial for immediate diagnosis and treatment. Coronavirus disease 2019 (COVID-19) has been associated with coagulopathy and thromboembolic events.

Case description: A 66-year-old woman presented with acute COVID-19 infection and primary adrenal insufficiency due to bilateral adrenal hemorrhage (BAH). She also had a renal vein thrombosis. Her past medical history revealed primary antiphospholipid syndrome (APLS). Four weeks after discharge she had no signs of COVID-19 infection and her polymerase chain reaction test for COVID-19 was negative, but she still needed glucocorticoid and mineralocorticoid replacement therapy. The combination of APLS and COVID-19 was probably responsible of the adrenal event as a “two-hit” mechanism.

Conclusions: COVID-19 infection is associated with coagulopathy and thromboembolic events, including BAH. Adrenal insufficiency is life threatening; therefore, we suggest that early adrenal axis testing for COVID-19 patients with clinical suspicion of adrenal insufficiency should be carried out.

Key Words: COVID-19, adrenal insufficiency, antiphospholipid syndrome, adrenal hemorrhage, renal vein thrombosis

Coronavirus disease 2019 (COVID-19) has been associated with coagulopathy and abnormal coagulation parameters (D-dimer, fibrin degradation products, and longer prothrombin time), which also predict mortality (1, 2). In addition, there is expert consensus and 1 retrospective study claiming that anticoagulation treatment decreases mortality in high-risk COVID-19 patients (3).

There are few data regarding hemorrhage in COVID-19 patients. Focal hemorrhage in lung tissue has been found in autopsies of patients who died of COVID-19...
Lung intraparenchymal bleeding and sporadic cases of extrapulmonary hemorrhage such as petechial bruises and upper gastrointestinal bleeding have been reported (5-7).

This case concerns a 66-year-old woman who presented with COVID-19 and primary adrenal insufficiency due to bilateral adrenal hemorrhage (BAH). Her past medical history revealed primary antiphospholipid syndrome (APLS).

**Case Presentation**

A 66-year-old female presented with fever, dyspnea, abdominal pain, vomiting, and nausea. Her symptoms began 5 days before her admission, and a polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 was positive. Her medical history included multiple abortions. Four months earlier she had undergone laparoscopic appendectomy due to acute appendicitis. Upon her emergency room admission, she presented with oxygen saturation of 94% (room air) and fever (38.3°C). Blood pressure was initially in the normal range but subsequently decreased. There was 1 episode of syncope. Physical examination revealed diffuse abdominal tenderness without acute abdomen signs. Her white cell count was 10 300/µL (normal range, 3600–10,000), with 85% neutrophils, 7.3% lymphocytes, 6.6% monocytes, and 0.7% eosinophils. The hemoglobin level was 12.1 g/dL (normal range, 12-16) and the platelet count was 222 000/µL (normal range, 150 000-450 000). C-reactive protein was 13 mg/dL (normal range, 0-0.5), creatinine level was 1.4 mg/dL (normal range, 0.52-1.04), and troponin level was 580 ng/L (normal range, 0-6). Activated partial thromboplastin time was 91 seconds (normal range, 25-38). Sodium level was 136 mEq/L on presentation (normal range, 135-145) and decreasing to 129 mEq/L after 6 hours. Potassium level was 3.5 mEq/L (normal range, 3.6-5.0). Liver function tests were normal.

Chest X-ray demonstrated peripheral confluent consolidation in the upper left lobe—a finding compatible with atypical pneumonia due to COVID-19. Due to remarkable abdominal tenderness the patient underwent contrast-enhanced dual-energy computed tomography (SOMATOM Dual Source, DRIVE, Siemens Healthcare) of the abdomen during the portal venous phase and postprocessing of virtual noncontrast and iodine map reconstructions. The adrenal glands appeared thick and enlarged with haziness of the surrounding peri-adrenal fat (Fig. 1A). The right adrenal gland had rounded appearance and measured 35 x 20 mm, the left adrenal gland was V shaped, with the medial limb measuring 38 x 6 mm and the lateral limb 42 x 7 mm. Both adrenal glands had an attenuation of 65 HU. There was no change in attenuation on the virtual noncontrast images or iodine map reconstruction, indicating lack of contrast enhancement and adrenal hemorrhage was suggested (Fig. 1B and 1C). A small filling defect was noted in the left renal vein, consistent with a nonobstructing thrombus (Fig. 2). Bilateral peripheral consolidations with patchy ground glass opacities with mild reticulation were demonstrated in the lung bases (Fig. 3). None of these findings were seen on a computed tomography scan 4 months earlier.

Due to the hyponatremia and the adrenal findings noted on the computed tomography scan, the baseline serum cortisol level was measured and found to be very low (<1 µg/dL). One hour after administration of intravenous cosyntropin 250 µg, the serum cortisol level remained low at the same level. Serum adrenocorticotropic hormone levels were high, 207 pmol/L (normal range, 1.6-13.9). Based on the clinical, laboratory, and radiographic findings, a diagnosis of primary adrenal insufficiency secondary to BAH was established, and steroid treatment was initiated (intravenous hydrocortisone, followed by prednisone 10 mg/day and fludrocortisone 0.1 mg/day). Shortly after initiation of treatment her blood pressure improved and she felt better. Her serum sodium levels had risen to normal range.

In addition, due to the history of repeat abortions and current adrenal hemorrhage, an antiphospholipid antibody profile blood test was ordered. The results showed triple-positive antiphospholipid antibody profile, including positive lupus anticoagulant, anticardiolipin immunoglobulin (Ig)M antibodies 76 units/mL (normal range, <7), anticardiolipin IgG antibodies 67 units/mL (normal range, <10), and anti-β2 glycoprotein 1 IgG antibodies 34 units/mL (normal range, <15). The antinuclear antibodies test was negative, and Complement 3 and Complement 4 values were within the normal range. Previous results from a different laboratory showed that anticardiolipin levels were elevated 3 years earlier too.

According to positive lupus anticoagulant, anticardiolipin antibodies, anti-β2 glycoprotein 1 antibodies, and the history of recurrent abortions, the diagnosis of APLS was confirmed. Anticoagulation treatment was delayed due to the recent active bleeding in the adrenal glands.

The patient was discharged after 11 days. Four weeks later she had a PCR test for COVID-19 that was negative and no signs for respiratory distress, but her morning cortisol levels were low and she still needed glucocorticoid and mineralocorticoid replacement therapy. She continues follow-up in the endocrinology clinic.

**Discussion**

This case concerns a 66-year-old female, diagnosed with APLS, who presented with mild COVID-19, BAH, and primary adrenal insufficiency.
BAH is a rare condition with an estimated incidence of around 1% in hospitalized patients, based on postmortem studies (8). Adrenal hemorrhage was described in meningococcemia (Waterhouse–Friderichsen syndrome) (9), *Haemophilus influenzae*, and other bacterial infections, as well as in viral infections including cytomegalovirus, parvovirus B19, and Epstein–Barr virus. Other predisposing conditions for BAH are postoperative state, anticoagulant therapy, and thromboembolic disease. Because of nonspecific clinical and laboratory findings that can easily be attributed to the underlying disease or postoperative complications, adrenal hemorrhage is rarely suspected. Most frequently described signs are abdominal pain, vomiting, fever, fatigue, hypotension, and confusion. Hypotension is not often seen before development of dramatic hypotension and shock (10).

APLS has been widely described as a predisposing condition to BAH in association of stress factors (11), and adrenal insufficiency can even be the first manifestation of APLS (12). The main proposed pathogenesis is an imbalance between increased arterial blood flow to the adrenal gland during a stressful event and limited venous drainage, leading to intraglandular vascular congestion, possible small venous thrombosis, and subsequent hemorrhage (10).

Although the hallmark of APLS is thromboembolic events, bleeding events are not uncommon. Coagulopathy and higher risk for thromboembolic events have been reported in COVID-19 patients. Three cases of APLS-like syndrome have been described (13). Compared with the presented case, all of them were 60 to 70 years old, and their serological tests were positive for anticardiolipin IgG, anti-β2 glycoprotein 1, and prolonged activated partial thromboplastin time. In contrast to the described case, they were in a critical condition and presented with multiple cerebral infarctions.

**Figure 1.** Axial contrast enhanced dual energy (DE) images at the level of the adrenal gland. (A) Mixed energy images demonstrate thickened adrenal glands (asterisk) with surrounding fat stranding (arrow). Both adrenal glands had an attenuation of 65 HU. (B, C) Virtual nonenhanced reconstruction (B) removes the iodine from the image and iodine map (C) accentuates the iodine. In both images, the adrenal glands are unchanged showing that there is no iodine uptake.
We assume that the discussed patient already had coagulopathy predisposition due to undiagnosed APLS. COVID-19 infection is also characterized by coagulopathy and thromboembolic events and put the patient at very high risk for thromboembolic events. The combination of both hits was probably responsible for the adrenal event. Eventually, microthrombosis of the adrenal plexus led to secondary bleeding.

Summary and conclusion

We have described a BAH and subsequently primary adrenal insufficiency in a patient with COVID-19. This presentation together with the patient’s history and relevant serologic tests led to the diagnosis of APLS. To our knowledge, this is the first report of BAH with primary adrenal insufficiency in a COVID-19 patient. Hypoadrenalism is life threatening and therefore we suggest to consider performing early adrenal axis testing for COVID-19 patients with clinical suspicion of adrenal insufficiency.

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Additional Information

Correspondence and Reprint Requests: Meir Frankel, Endocrinology Unit, Shaare Zedek Medical Center, POB 3235, Jerusalem 9103102, Israel. E-mail: meirf@szmc.org.il.

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References

1. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel Coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.
2. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020;95(7):834-847.
3. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099.
4. Yao XH, Li TY, He ZC, et al. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi. 2020;49(5):411-417.
5. Joob B, Wiwanitkit V. Hemorrhagic problem among the patients with COVID-19: clinical summary of 41 Thai infected patients. Clin Appl Thromb Hemost. 2020;26:1076029620918308.
6. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69(6):997-1001.
7. Vu D, Ruggiero M, Choi WS, et al. Three unsuspected CT diagnoses of COVID-19. Emerg Radiol. 2020;27(3):229-232.
8. Xarli VP, Steele AA, Davis PJ, et al. Adrenal hemorrhage in the adult. Medicine (Baltimore). 1978;57(3):211-221.
9. Migeon CJ, Kenny FM, Hung W, et al. Study of adrenal function in children with meningitis. Pediatrics 1967;40(2):163-183.
10. Arnason JA, Graziano FM. Adrenal insufficiency in the antiphospholipid antibody syndrome. Semin Arthritis Rheum. 1995;25(2):109-116.
11. Ramon I, Mathian A, Bachelot A, et al. Primary adrenal insufficiency due to bilateral adrenal hemorrhage-adrenal infarction in the antiphospholipid syndrome: long-term outcome of 16 patients. J Clin Endocrinol Metab. 2013;98(8):3179-3189.
12. Satta MA, Corsello SM, Della Casa S, et al. Adrenal insufficiency as the first clinical manifestation of the primary antiphospholipid antibody syndrome. Clin Endocrinol (Oxf). 2000;52(1):123-126.
13. 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.