

# CASE REPORT

Nagoya J. Med. Sci. 83. 883–891, 2021  
doi:10.18999/nagjms.83.4.883

## A patient with mild respiratory COVID-19 infection who developed bilateral non-hemorrhagic adrenal infarction

Yuki Asano<sup>1</sup>, Tomomichi Koshi<sup>1</sup>, Asami Sano<sup>1</sup>, Takashi Maruno<sup>2</sup>,  
Makoto Kosaka<sup>2</sup>, Yoshitaka Yamazaki<sup>2</sup>, Ako Oiwa<sup>3</sup> and Yutaka Nishii<sup>1</sup>

<sup>1</sup>*Department of Endocrinology and Metabolism Internal Medicine, Nagano Municipal Hospital, Nagano, Japan*

<sup>2</sup>*Center of Infectious Diseases, Nagano Prefectural Shinshu Medical Center, Suzaka, Japan*

<sup>3</sup>*Department of Diabetes, Endocrinology and Metabolism, Division of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan*

### ABSTRACT

A 76-year-old woman was admitted to the emergency room of Nagano Municipal Hospital with the complain of severe back pain. Chest and abdominal enhanced computed tomography scans showed bilateral adrenal infarction and minute pulmonary nodules, but she had no respiratory symptoms. After admission, a family member of the patient was found to have been in close contact with a coronavirus disease 2019 (COVID-19) patient. Thus, polymerase chain reaction and antigen tests of severe acute respiratory syndrome coronavirus 2 were conducted, and both tests returned positive. D-dimer levels were normal on admission but increased 2 days thereafter. Anticoagulation therapy and steroid replacement were started, and the patient improved over about two weeks. One month after the onset of adrenal infarction, a rapid adrenocorticotropic hormone loading test was conducted, which revealed that the primary adrenal insufficiency due to adrenal infarction might have been caused by the COVID-19 infection. This case was rare and suggestive of adrenal infarction with COVID-19, which usually presents at the severe stage. In patients with COVID-19, attention should be paid to the onset of thrombosis, even with mild respiratory infection. We also suggest that patients with thrombosis should be suspected of having COVID-19 even in the absence of respiratory infectious symptoms in a situation of COVID-19 epidemic.

Keywords: COVID-19, adrenal infarction, thrombosis

#### Abbreviations:

ACTH: adrenocorticotropic hormone

COVID-19: coronavirus disease 2019

Cre: creatinine

CT: computed tomography

eGFR: estimated glomerular filtration rate

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

PCR: polymerase chain reaction

WBC: white blood cell count

This is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Received: April 13, 2021; accepted: June 18, 2021

Corresponding Author: Ako Oiwa, MD, PhD

Department of Diabetes, Endocrinology and Metabolism, Division of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan

Tel: +81-263-37-2686, Fax: +81-263-37-2710, E-mail: akooiwa@shinshu-u.ac.jp

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was reported for the first time in Wuhan, China in December 2019, and as of March 2021, the pandemic continues worldwide. It has been reported that thrombosis and adrenal infarction are likely to occur as a complication of COVID-19,<sup>1</sup> and in severe COVID-19 patients, respectively.<sup>2</sup> We report a rare case of bilateral non-hemorrhagic adrenal infarction with mild COVID-19 without respiratory symptoms, and with minute pneumonia lesions in the chest computed tomography (CT) scans.

## CASE REPORT

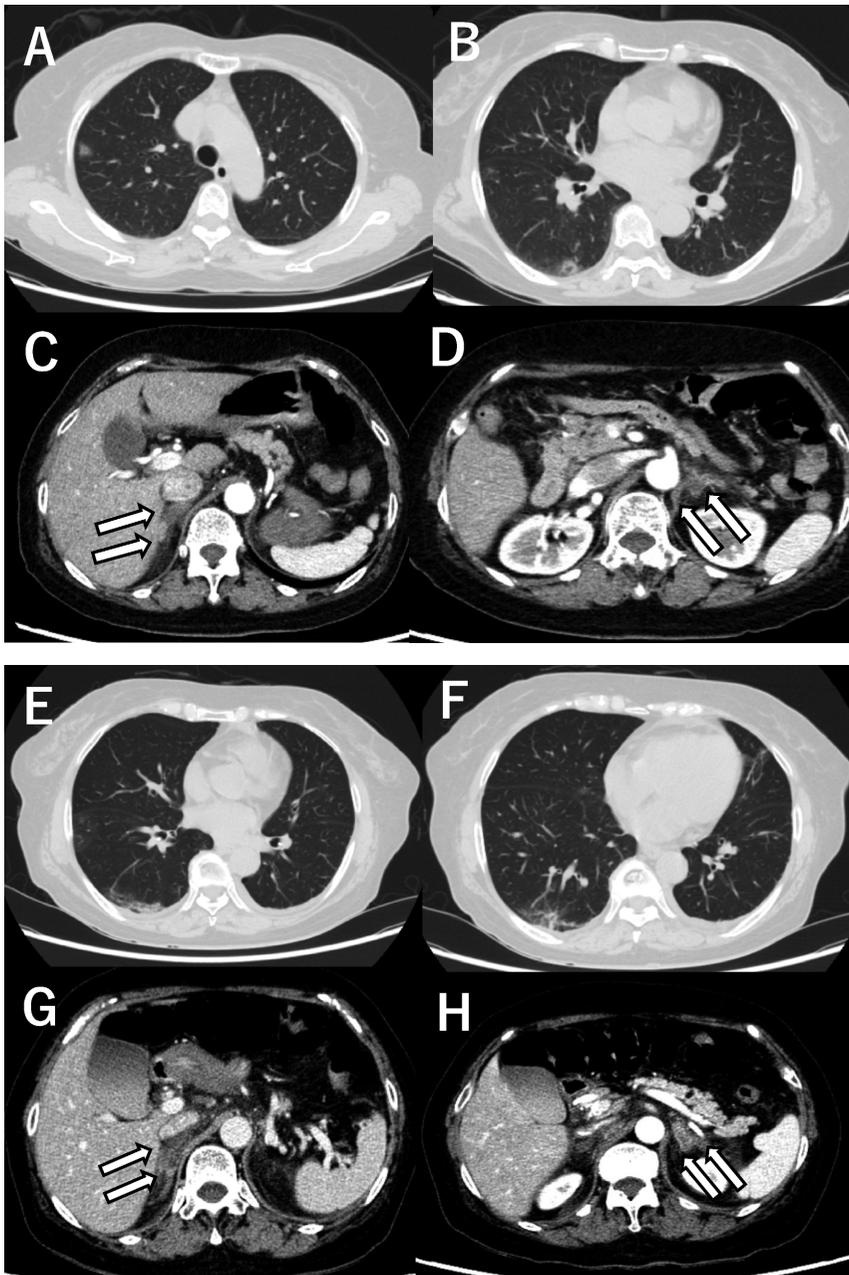
The patient was a 76-year-old woman with a medical history of Sjögren's syndrome, although she was being followed-up for symptomatic treatment only. She developed cough at the end of July 2020, after which her condition naturally improved. A few days later, back pain appeared and she vomited about 10 times; therefore, she visited the emergency room of Nagano Municipal Hospital. There were no remarkable blood tests or chest and abdominal enhanced CT scan findings that might have explained her symptoms; hence, the patient was sent back home. However, the next day, the patient was urgently hospitalized because of exacerbation of the back pain and the presence of black vomitus. There were still no abnormal blood test findings as before, but following careful observation of the chest and abdominal enhanced CT scans conducted the previous day, bilateral adrenal infarction and minute pulmonary nodules scattered in both lung fields were found (Fig. 1 A–D).

The patient was afebrile on admission. Her blood pressure was 178/93 mmHg, pulse rate was 82 beats/min and regular, and oxygen saturation was 97 % in room air. The level of consciousness using the Glasgow Coma Scale eye opening, verbal, and motor responses was determined as E4V5M6. The respiratory sounds were normal. Although clear bilateral back pain was noted, there was no costovertebral angle tenderness. Hemorrhagic spots and efflorescence were not observed on the skin of the whole body.

The result of the blood test performed on admission showed a blood cortisol, adrenocorticotropic hormone (ACTH), Na, K, and eosinophil levels of 37.6 µg/dL; 40.3 pg/mL; 142 mmol/L; 3.7 mmol/L; and 0.0%, respectively, and no findings suggestive of adrenal insufficiency (Table 1). There were slight increases in the parameters suggesting inflammation, which included a C-reactive protein level of 1.04 mg/dL and a leukocyte count of 11,560 /µL. The coagulation markers, including D-dimer, were normal. The results of both lupus anticoagulant and anti-cardiolipin antibody tests were negative. No clear abnormal shadows were observed on the chest radiographs. The chest and abdominal CT scans showed multiple minute ground-glass shadows in the right lung (Fig. 1 A, B). The scans also showed a slight swelling of both adrenal glands containing lesions with partially poor contrast enhancement of the parenchyma and elevated peripheral concentrations (Fig. 1 C, D). A lower limb venous ultrasound revealed no clear venous thrombosis.

On the zero day of illness, adrenal insufficiency, respiratory infection, and clear thrombotic tendencies were not suspected; therefore, follow-up observations were conducted. The intense back pain was thought to be caused by the adrenal infarction, and it was treated with an intramuscular injection of pentazocine hydrochloride.

On the first day of illness, since a fever of approximately 38°C was observed, the intravenous administration of 6 g/day of sulbactam / ampicillin (ABPC/SBT) was started based on the sus-



**Fig. 1** Transition of CT images with the course of the disease

The chest and abdominal CT the previous day on admission (A–D). Multiple minute ground-glass shadows are shown in the right lung. Swellings of both adrenal glands are observed, and the contrast enhancement of the parenchyma is partially poor (C, D). C shows the right and D the left adrenal glands.

The chest and abdominal CT on the second day of illness (E–H). New ground glass shadows are observed, and the size of existing shadows is increased (E, F). The area of the diminished contrast effect of the bilateral adrenal glands is expanded (G, H).

CT: computed tomography

**Table 1** Laboratory data on admission

UN	12	mg/dL	PT	12.7	sec
Cre	0.5	mg/dL	PT-INR	0.96	
eGFR	88.3	mL/min/1.73 m <sup>2</sup>	APTT	25.4	sec
AST	23	U/L	D-dimer	0.9	µg/mL
ALT	14	U/L			
CRP	1.04	mg/dL	anti ds-DNA antibody	10	IU/mL (<10)
Na	142	mmol/L	lupus anticoagulant	1.27	IU/mL (≤1.2)
K	3.7	mmol/L	anti-cardiolipin antibody	5	U/mL (<10)
Cl	105	mmol/L	protein C activity	105	% (64–146)
Glu (casual)	174	mg/dL	protein S activity	80	% (56–126)
WBC	11560	/µL	CYFRA	1.5	ng/mL (≤3.5)
(NEUT)	88.5	%	SCC	1.4	ng/mL (≤2.5)
(LYM)	5.5	%			
(EOS)	0	%	Cortisol (casual)	37.6	µg/dL
RBC	488×10 <sup>4</sup>	/µL	ACTH (casual)	40.3	pg/mL
HGB	14.7	g/dL			
HCT	43.8	%			
PLT	33.5×10 <sup>4</sup>	/µL			

UN: urea nitrogen

Cre: creatinine

eGFR: estimated glomerular filtration rate

AST: aspartate amino transferase

ALT: alanine aminotransferase

CRP: C-reactive protein

Na: sodium

K: potassium

Cl: chloride

Glu: glucose

WBC: white blood cell count

NEUT: neutrophils

LYM: lymphocyte

EOS: eosinophils

RBC: red blood cells

HGB: hemoglobin

HCT: hematocrit

PLT: platelet

PT: prothrombin time

PT-INR: PT international normalized ratio

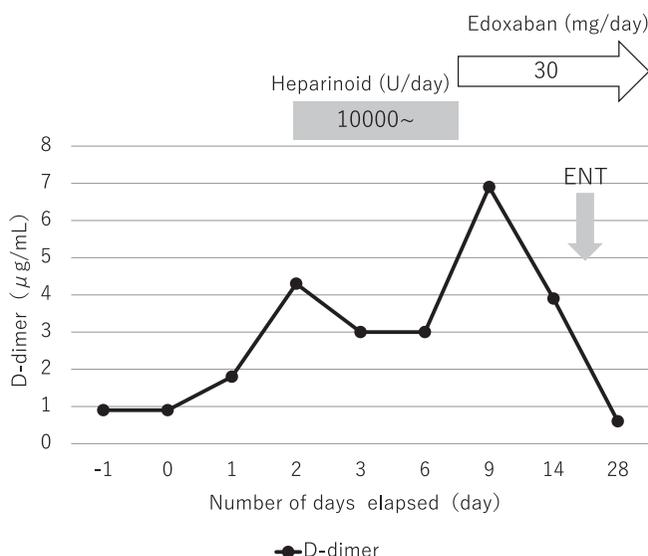
APTT: activated partial thromboplastin time

CYFRA: cytokeratin fragments

SCC: squamous cell carcinoma

ACTH: adrenocorticotropic hormone

## Adrenal infarction in COVID-19



**Fig. 2** Transition of D-dimer level

D-dimer level was normal on admission. From the first day of illness, it became elevated. On the second day of illness, anticoagulation therapy was started.

picion of pneumonia. Based on early-morning blood cortisol of 29.7 µg/dL and ACTH of 176.6 pg/mL, the secretion of cortisol was thought to be insufficient, and 25 mg/dose x 2 doses/day of hydrocortisone were administered. D-dimer became slightly increased to 1.8 µg/dL (Fig. 2). On the same day of the patient's admission, in the night, a family member of the patient was found to have been in close contact with a COVID-19 patient; hence, the patient was transferred to a negative pressure chamber.

On the second day of illness, PCR and antigen tests of SARS-CoV2 were conducted, and both tests returned positive. There were still no symptoms suggesting a worsening respiratory status, such as dyspnea, cough, and poor oxygenation. According to the rule that hydrocortisone must be administered sufficiently on sick days in patients who may have adrenal insufficiency, hydrocortisone was increased to 50 mg/dose every six hours. The D-dimer level increased to 4.3 µg/mL (Fig. 2). Chest and abdominal enhanced CT showed an increase in the ground glass shadows in the upper right lobe compared to those taken 3 days ago, and new ground glass shadows with indistinct boundaries were observed in the lower right and upper left lobes of the lung (Fig. 1 E, F). No new coarse thrombosis was noted, but we suspected that the adrenal infarction might have progressed due to the diminished contrast effect of the bilateral adrenal glands (Fig. 1 G, H). After no clear bleeding tendencies were confirmed, continuous intravenous infusion of heparin (10000 U/day) was started.

On the third day of illness, the D-dimer level decreased to 3.0 µg/mL (Fig. 2), and back pain showed a tendency to improve. The dose of heparin was adjusted targeting activated partial thromboplastin time (APTT). As before, no respiratory symptoms were observed.

On the seventh day of illness, the hydrocortisone dose was reduced to 30 mg/day and she was switched to oral medication. Additionally, continuous intravenous infusion of heparin was discontinued, and the drug was switched to 30 mg/day of edoxaban.

On the 18<sup>th</sup> day of illness, the patient was discharged from the hospital following an assessment of no infectiousness.

On the 28<sup>th</sup> day of illness, a rapid ACTH loading test was conducted to evaluate the adrenal function. Primary adrenal insufficiency was suspected by the results of the test showing cortisol levels of 4.3 µg/dL before and 6.5 µg/dL after loading, which implied that the response of cortisol to ACTH had almost disappeared. Therefore, oral administration of hydrocortisone was continued at 25 mg/day.

## DISCUSSION

The main causes of adrenal infarction are antiphospholipid antibody syndrome<sup>3,4</sup> and pregnancy. Other rare differential diagnoses include heparin-induced thrombocytopenia and myelodysplastic syndrome. It is thought that the onset of adrenal infarction in this patient was triggered by COVID-19. A large amount of hydrocortisone was administered to this patient immediately after the suspected adrenal infarction, which made an evaluation of her adrenal function impossible. After discharge, one month after the onset of adrenal infarction, the rapid ACTH loading test suggested the primary adrenal insufficiency. It was thought that the test results were not influenced by the oral administration of hydrocortisone which suppresses the secretion of ACTH and cortisol. This is because the latest oral administration of hydrocortisone occurred about 24 hours before the test was performed, which possibly meant that the oral hydrocortisone was no longer working. As there is no consensus on the amount or duration of administration of hydrocortisone that suppresses endogenous cortisol secretion,<sup>5</sup> there is a possibility that the prescription of hydrocortisone at 25 mg daily for one month had caused the decreasing response of cortisol to a rapid ACTH loading test. However, it would be unlikely that this level of total hydrocortisone dose suppressed endogenous cortisol secretion completely as in this result.

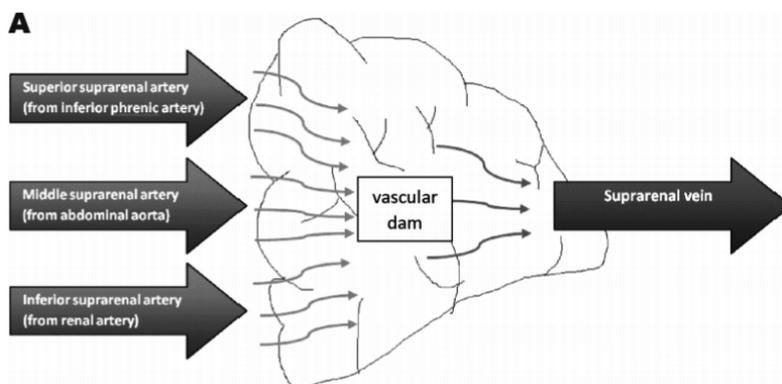
As reported, patients with COVID-19 are prone to thrombotic events.<sup>1</sup> In particular, the report indicated that thrombotic complications in severely ill patients occurred at a high frequency of 31% regardless of whether there were of venous or arterial nature.<sup>1</sup> It was also reported in a retrospective cohort analysis that, 51 out of 219 severely ill COVID-19 patients developed acute adrenal infarction.<sup>2</sup> From the above, it is believed that the more severe the infection, the more likely it is for thrombosis and adrenal infarction to develop. This patient was a rare case of adrenal infarction that occurred with mild COVID-19 infection without respiratory symptoms. The patient had only minute pneumonia lesions in the chest CT scans and no other thrombosis complication than adrenal infarction. This patient presented quite differently from previously reported cases of adrenal infarction due to SARS-CoV-2 infection.<sup>2,6</sup>

According to the International Society of Thrombosis and Hemostasis (ISTH) guidelines,<sup>7</sup> D-dimer values may be considered most significant in reflecting the severity of complications due to coagulopathy in COVID-19. Hospitalization is recommended when D-dimer values increase three- to four-fold even if there are no other concerns because it implies high risks of coagulopathy and disseminated intravascular coagulopathy. However, there are cases such as in the present patient in which increases in D-dimer values may occur several days after the onset. Therefore, both the severity of infection and the necessity of hospitalization should be considered comprehensively from many factors such as the clinical findings, blood tests, urine tests, CT scans, and so on.

The ISTH guidelines recommended that when thrombosis complications related to COVID-19 are identified with no hemorrhagic lesions, anticoagulation therapy based on a continuous intravenous administration of heparin or oral warfarin should be considered. This patient was well at discharge, due to the early start of anticoagulation therapy, administered as soon as possible.

Thrombosis by COVID-19 is associated with macrophages, inflammatory cytokines, and

## Adrenal infarction in COVID-19



**Fig. 3** Adrenal vascular structure<sup>13</sup>

coagulation cascades.<sup>8,9</sup> Other reports have indicated that direct damage to the vascular endothelial cells by SARS-CoV-2 activates the coagulation system. SARS-CoV-2 is thought to have an affinity for cells that express angiotensin converting enzyme II (ACE II).<sup>10</sup> ACE II is expressed in cells throughout the body, but its expression rates vary according to the organ. ACE II is expressed not only in alveolar type II cells but also in epithelial cells of the upper esophagus, ileum, and colon; the endothelial cells of arteries and veins; and the arterial smooth muscle cells.<sup>11</sup> Furthermore, in endocrine-related organs, ACE II is expressed in the adrenal gland, pancreas, thyroid gland, testis, ovary, and pituitary gland.<sup>12</sup>

The adrenal gland is considered vulnerable to hemorrhage and infarction, which could be due to the anatomy of the adrenal vasculature.<sup>13</sup> A large amount of blood is supplied to the adrenal gland from the inferior phrenic, celiac, and renal arteries which form the subcapsular artery plexus. A “vascular dam”<sup>13</sup> is formed by 50 to 60 small adrenal branches. The subsequent flow of blood all at once into the single adrenal vein<sup>13,14</sup> can cause blood flow stagnation, which is thought to increase the possibility of thrombosis and hemorrhage (Fig. 3).

Furthermore, ACTH and adrenaline play additional roles in the development of thrombosis. Under severe stress, including sepsis, secretion of ACTH and adrenaline increases. Elevated ACTH increases the intravascular pressure by increasing the adrenal blood flow, which leads to infarction and hemorrhage.<sup>15</sup> This situation is further accentuated by adrenaline acting on platelet aggregation in the adrenal veins.

It is retrospectively reported that the adrenal gland infarct is bilateral in 88% of patients who develop adrenal infarction due to COVID-19.<sup>2</sup> Most adrenal infarctions in pregnancy are unilateral,<sup>16</sup> whereas Waterhouse-Friderichsen syndrome (WFS), primarily caused by bacterial infections such as meningococci, is also known to cause bilateral adrenal hemorrhage.<sup>17</sup> Both bilateral adrenal infarction and hemorrhage due to COVID-19 and WFS may be explained not only by a shared mechanism of adrenal anatomy but also by the shared physiological response to the stress due to infection.

## CONCLUSION

We report a patient with a rare case of a very mild COVID-19 respiratory infection who developed bilateral non-hemorrhagic adrenal infarction. Anticoagulation therapy should be performed immediately when thrombotic tendencies are observed, to prevent an increase in the

severity of the disease, including multiple organ failure.

Even if SARS-CoV-2 infection presents with mild form, based on several findings, attention should be given to the various complications, particularly systemic thrombosis, including adrenal infarction. In other words, when examining a patient with thrombosis, it is important to suspect COVID-19 infection, even in the absence of respiratory infectious symptoms when COVID-19 pandemic exists.

#### ACKNOWLEDGEMENTS

We would like to thank Editage (www.editage.com) for English language editing.

#### INFORMED CONSENT

This patient has provided permission to publish her features of this case, and the identity of the patient has been protected.

#### DECLARATION OF INTEREST

None.

#### REFERENCES

- 1 Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145–147. doi:10.1016/j.thromres.2020.04.013.
- 2 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. doi:10.1007/s00330-020-07226-5.
- 3 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. doi:10.1210/jc.2012-4300.
- 4 Espinosa G, Santos E, Cervera R, et al. Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients. *Medicine (Baltimore).* 2003;82(2):106–118. doi:10.1097/00005792-200303000-00005.
- 5 Schlaghecke R, Kornely E, Santen RT, Ridderskamp P. The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. *N Engl J Med.* 1992;326(4):226–230. doi:10.1056/NEJM199201233260403.
- 6 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. doi:10.1259/bjrcr.20200075.
- 7 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost.* 2020;18(5):1023–1026. doi:10.1111/jth.14810.
- 8 Mcgonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol.* 2020;2(7):e437–e445. doi:10.1016/S2665-9913(20)30121-1.
- 9 Tan CW, Low JGH, Wong WH, Chua YY, Goh SL, Ng HJ. Critically ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. *Am J Hematol.* 2020;95(7):E156–E158. doi:10.1002/ajh.25822.
- 10 Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). *Clin Gastroenterol Hepatol.* 2020;18(7):1636–1637. doi:10.1016/j.cgh.2020.03.043.
- 11 Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J*

- Pathol.* 2004;203(2):631–637. doi:10.1002/path.1570.
- 12 Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. *J Endocrinol Invest.* 2020;43(7):1027–1031. doi:10.1007/s40618-020-01276-8.
  - 13 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. doi:10.1530/eje.1.02002.
  - 14 You JY, Fleischer N, Abraham SB. Evolving adrenal dysfunction after bilateral adrenal infarction: A case report. *AACE Clin Case Rep.* 2019;5(6):e334–e339. doi:10.4158/ACCR-2019-0167.
  - 15 Stark E, Varga B, Acs Z, Papp M. Adrenal blood flow response to adrenocorticotrophic hormone and other stimuli in the dog. *Pflugers Arch Gesamte Physiol Menschen Tiere.* 1965;285(4):296–301. doi:10.1007/BF00363229.
  - 16 Glomski SA, Guenette JP, Landman W, Tatli S. Acute nonhemorrhagic adrenal infarction in pregnancy: 10-year MRI incidence and patient outcomes at a single institution. *AJR Am J Roentgenol.* 2018;210(4):785–791. doi:10.2214/AJR.17.18739.
  - 17 Karki BR, Sedhai YR, Bokhari SRA. Waterhouse-Friderichsen syndrome. <https://www.statpearls.com/articlelibrary/viewarticle/31309/>. StatPearls Publishing, Treasure Island (FL). Accessed Jun 30, 2020.