Bilateral adrenal hemorrhage in Coronavirus disease 2019 patient: A case report

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Abstract

Context: Bilateral adrenal hemorrhage is a rare condition with potentially life-threatening consequences 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 decription: A 66-years-old woman presented with acute COVID-19 infection and primary adrenal insufficiency due to bilateral adrenal hemorrhage (BAH). She had also a renal vein thrombosis. Her past medical history revealed primary antiphospholipid syndrome (APLS). 4 weeks after discharge she had no signs of COVID-19 infection and her PCR 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 to consider performing early adrenal axis testing for COVID-19 patients with clinical suspicion of adrenal insufficiency.

Keywords: COVID-19, Adrenal insufficiency, Antiphospholipid syndrome, Adrenal hemorrhage, Renal vein thrombosis

Introduction

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 an expert consensus and one retrospective study, claiming that anticoagulation treatment decreases mortality in high-risk COVID-19 patients [3].

There are scarce data regarding hemorrhage in COVID-19 patients. Focal hemorrhage in lung tissue has been found in autopsies of patients who died of COVID-19 (4). 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. 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 five days before her admission, and a polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was positive. Her medical history included multiple abortions. Four months earlier she underwent laparoscopic appendectomy due to acute appendicitis. Upon her emergency room admission, she presented with an oxygen saturation of 94% (room air) and fever (38.3^{o}C). Blood pressure was initially in the normal range but subsequently decreased .There was one episode of syncope. Physical examination revealed diffuse abdominal tenderness without acute abdomen signs. Her white-cell count was 10,300 per microliter (normal range, 3,600-10,000), with 85% neutrophils, 7.3% lymphocytes, 6.6% monocytes and 0.7% eosinophils. The hemoglobin level was 12.1 gram per deciliter (normal range, 12-16) and the platelet count was 222,000 per microliter (normal range, 150,000-450,000). C-reactive protein was 13

milligram per deciliter (normal range, 0-0.5), creatinine level was 1.4 milligram per deciliter (normal range, 0.52-1.04) and troponin level 580 nanogram per liter (normal range, 0-6). Activated partial thromboplastin time (aPTT) was 91 seconds (normal range, 25-38). Sodium level was 136 milliequivalent per liter (mEq/L) on presentation (normal range, 135-145) and decreased to 129 mEq/L after 6 hours. Potassium level was 3.5 mEq/L (normal range, 3.6-5.0) and 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 CT (DECT), (SOMATOM Dual Source, DRIVE, Siemens Healthcare) of the abdomen during the portal venous phase and post-processing of Virtual Non Contrast (VNC) and iodine map reconstructions. The adrenal glands appeared thick and enlarged with haziness of the surrounding peri-adrenal fat (Figure 1 A). The right adrenal had rounded appearance and measured 35*20 mm, the left adrenal was V shaped with the medial limb measuring 38*6 mm and lateral limb 42*7 mm. Both adrenal glands had an attenuation of 65HU. There was no change in attenuation on the VNC images or iodine map reconstruction, indicating lack of contrast enhancement and adrenal hemorrhage was suggested (Figures 1 B and C). Small filling defect was noted in the left renal vein, consistent with non-obstructing thrombus (Figure 2). Bilateral peripheral consolidations with patchy ground glass opacities with mild reticulation were demonstrated in the lung bases (Figure 3). None of these findings were seen on a CT four months earlier.

Due to the hyponatremia and the adrenal findings noted on the CT, baseline serum cortisol level was measured and found very low (<1 microgram per deciliter). One hour after administration of intravenous Cosynotropin 250 microgram, serum cortisol level remained low at the same level. Serum adrenocorticotropic hormone (ACTH) levels were high, 207 picomol per liter (normal range, 1.6-13.9). Based on the clinical, laboratory and radiographic findings, a diagnosis of primary adrenal insufficiency secondary to bilateral adrenal hemorrhage had been established, and steroid treatment

was initiated (intravenous hydrocortisone, followed by prednisone 10 milligram/day and fludrocortisone 0.1 milligram/day). Shortly after initiation the 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, antiphospholipid antibody (APLA) profile blood test was ordered. The results showed triple-positive APLA profile, including positive lupus anticoagulant (LAC), anti-cardiolipin IgM antibodies 76 units per milliliter (normal range, <7), anti-cardiolipin IgG antibodies 67 units per milliliter (normal range, <10), and anti- β2 glycoprotein 1 (β2gp1) IgG antibodies 34 units per milliliter (normal range, <15). Antinuclear antibodies (ANA) test was negative, and Complement 3 (C3) and Complement 4 (C4) values were within the normal range. Previous results from a different laboratory showed that Anti-cardiolipin levels were elevated 3 years earlier too.

According to positive LAC, anti-cardiolipin antibodies, anti-β2gp1 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 adrenals.

The patient was discharged after 11 days. 4 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 endocrinology clinic.

Discussion

This case concerns a 66-year-old female, diagnosed with APLS, that presented with mild COVID-19, bilateral adrenal hemorrhage (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 influenza 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 complication, 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 be even 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 event have been reported in COVID-19 patients. Three cases of APLS-like syndrome have been described [13]. Compared to the presented case, all of them were 60-70-year-old, and their serological tests were positive for anti-cardiolipin IgG, anti beta-2 glycoprotein I, and prolonged aPTT. In contrast to the described case, they were in a critical condition and presented with multiple cerebral infarctions.

We assume that the discussed patient had already 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 of the adrenal event. Eventually, microthrombosis of the adrenal plexus led to secondary bleeding.

Summary and conclusion

We 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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Figure Legends:

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 65HU.

B, C :Virtual non-enhanced (VNC) 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.

Figure 2. Axial (A) and Coronal (B) contrast enhanced images demonstrate a mall filling defect in the left renal vein (arrows) consistent with thrombus.

Figure 3. Axial images in lung windowing demonstrate peripheral reticulation and ground glass opacities, typical findings in COVID 19.

Figure 1A

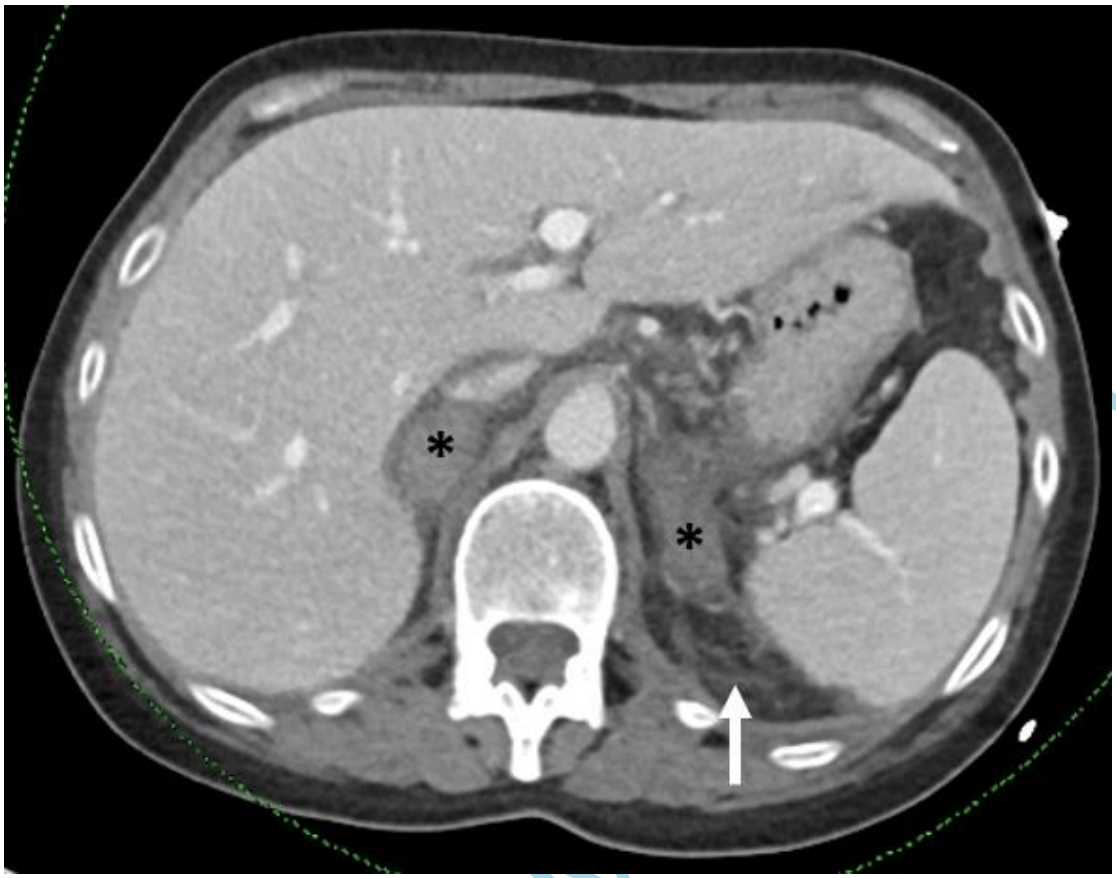

Figure 1B

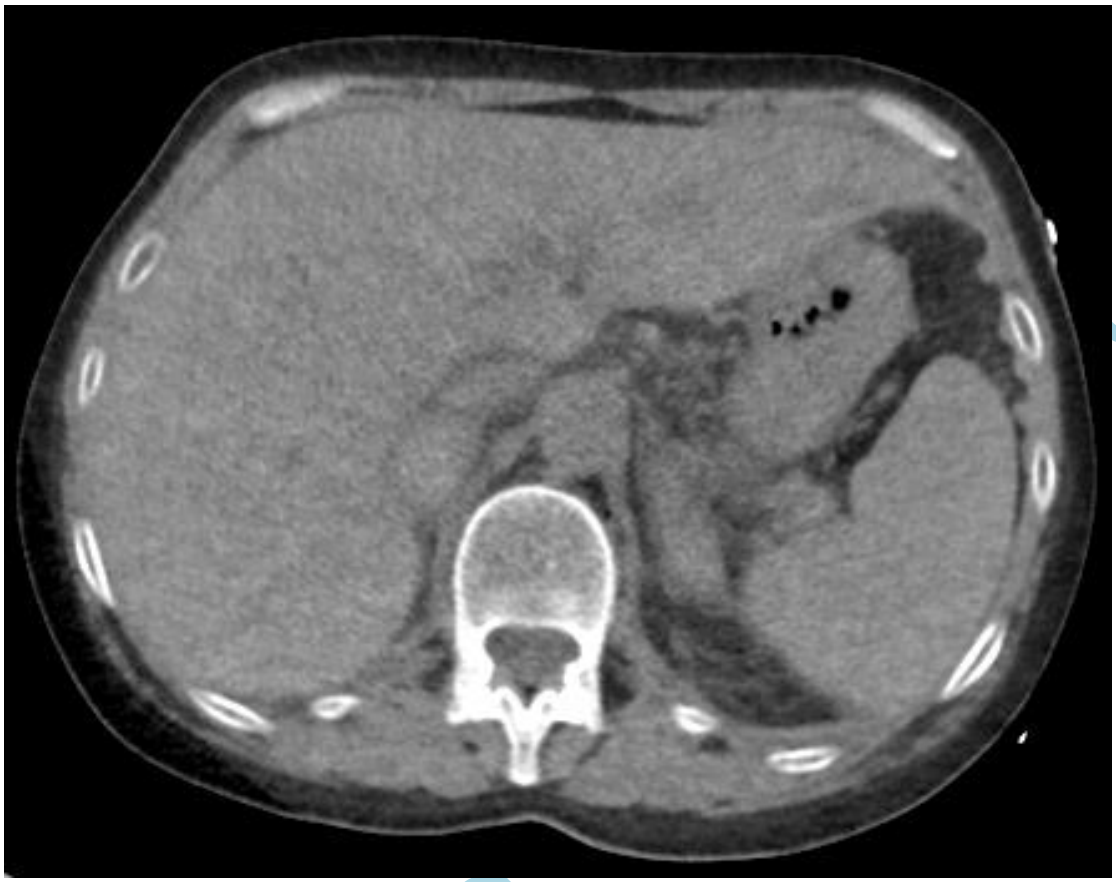

Figure 1C

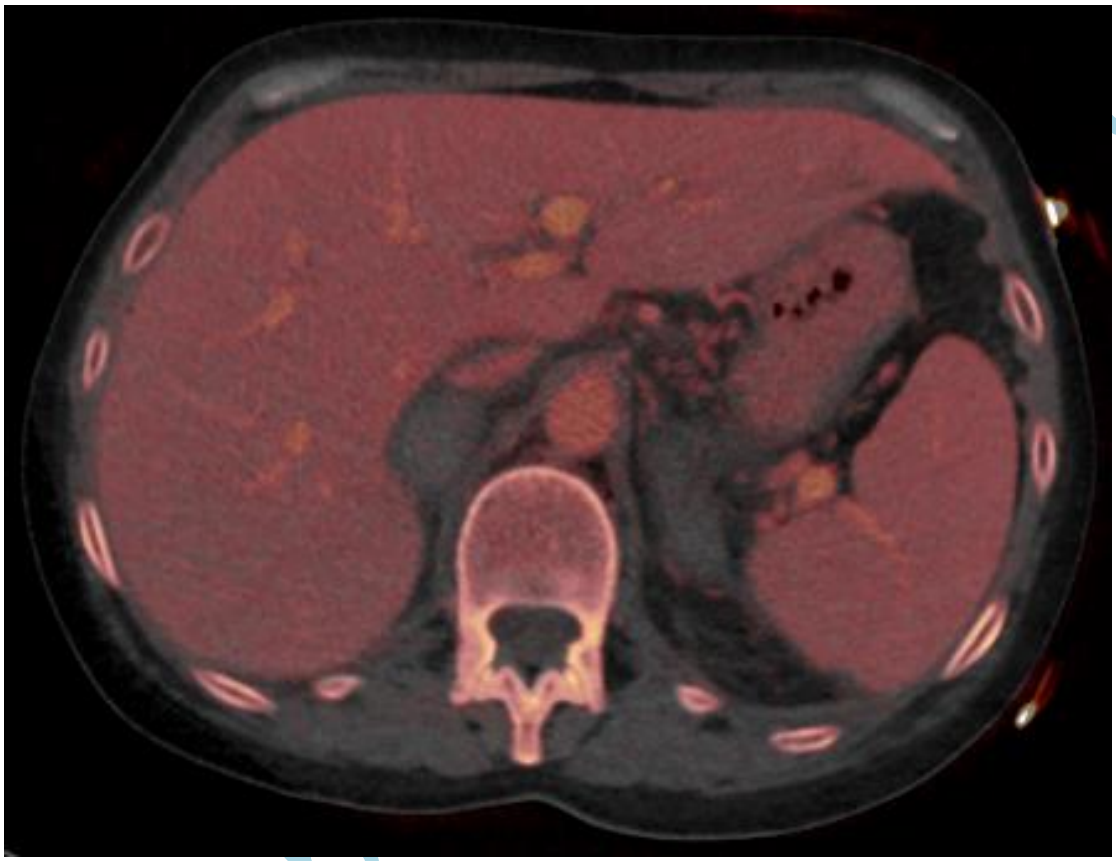

Figure 2A

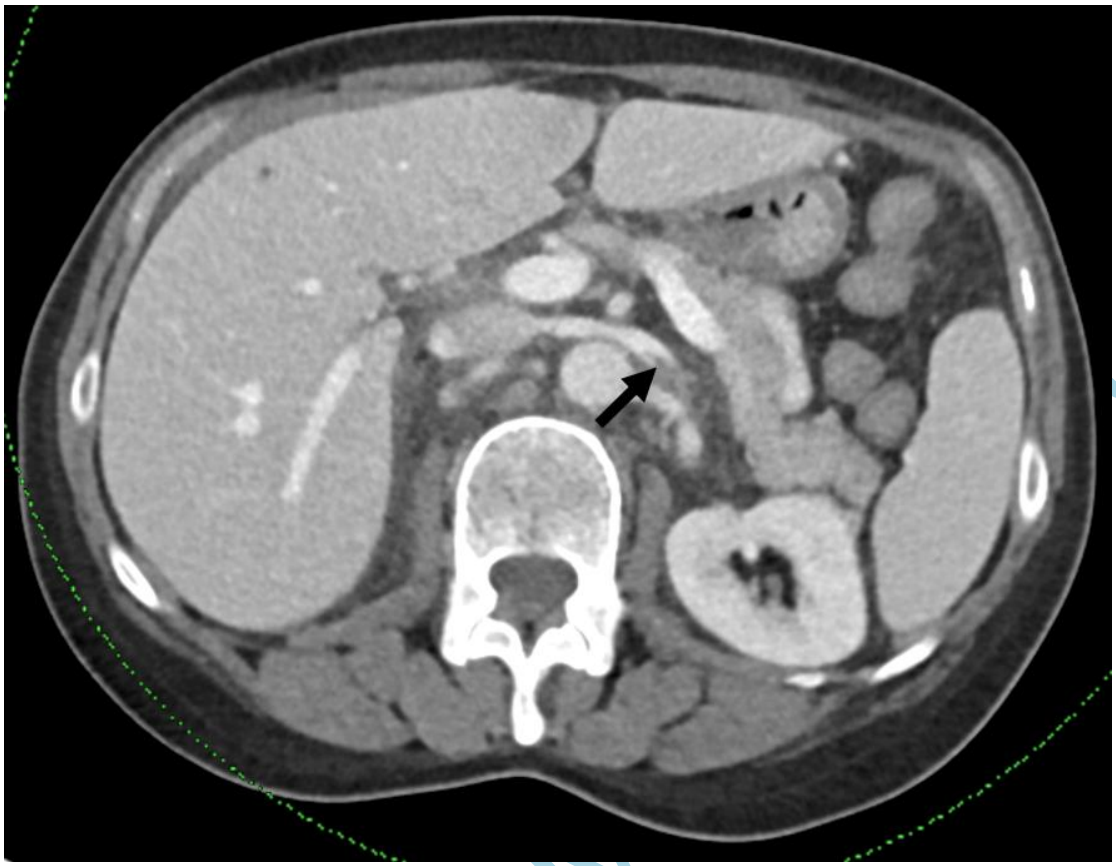

Figure 2B

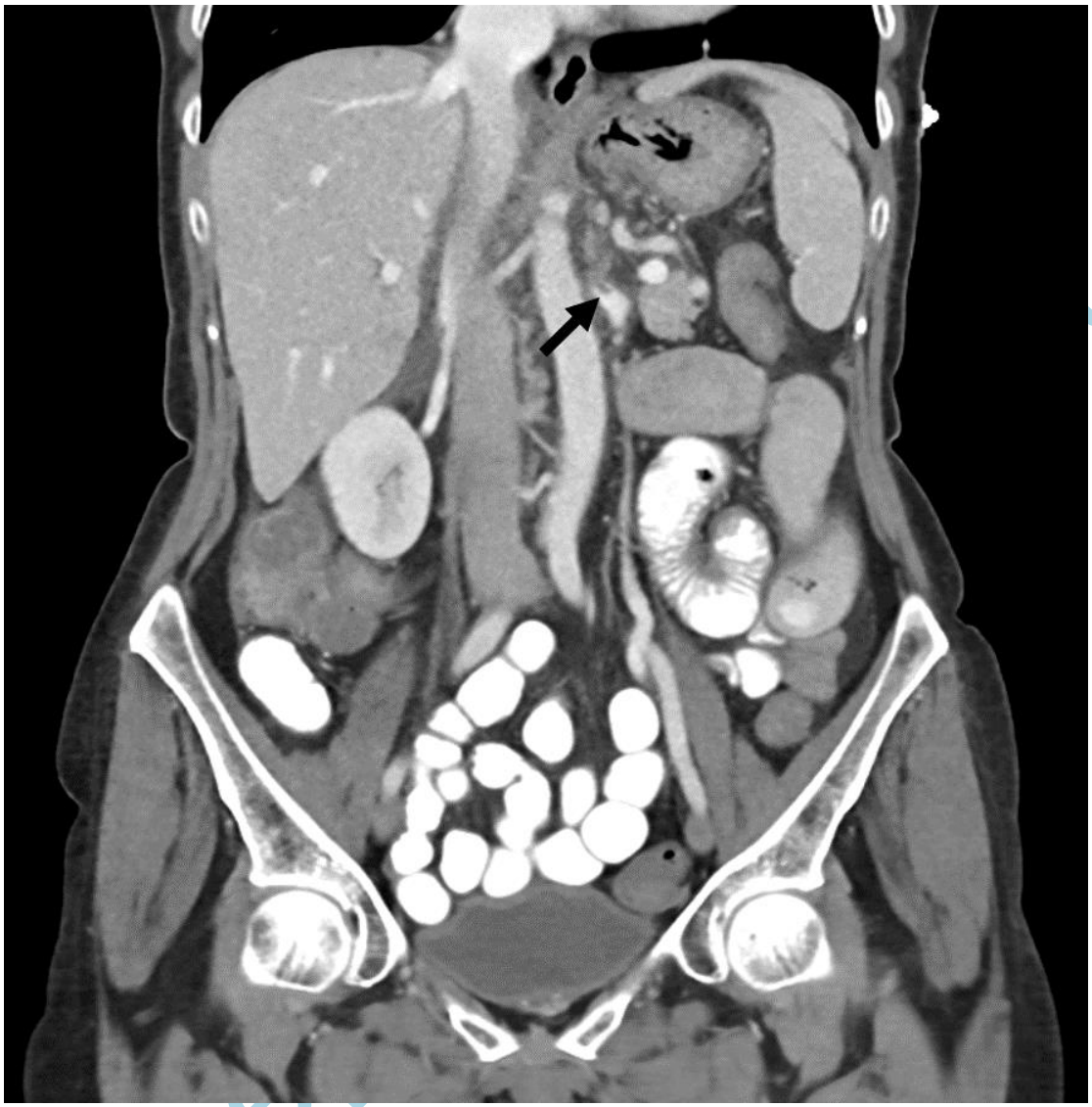

Figure 3