Emergence of Autoimmune Type 1 Diabetes and Acute Adrenal Crisis Following COVID-19

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Abstract

Objective: Several case reports have indicated a possible link between Coronavirus Disease 2019 (COVID-19) and new-onset autoimmune disorders while co-precipitation of autoimmune type 1 diabetes and Addison's disease has never been reported to date.

Case Description: A 60-year-old male presented with extreme fatigue and weight loss three weeks after testing positive for COVID-19. The course of COVID-19 was mild, without pulmonary involvement. The patient showed symptoms and laboratory signs of new-onset diabetes without ketoacidosis and acute primary adrenal insufficiency, latter of which was confirmed with an ACTH stimulation test. GAD-65 antibody and antibodies to the adrenal cortex were positive in high titers, and the patient also had primary hypothyroidism associated with autoimmune thyroiditis. Previous medical records of the patient revealed no hyperglycemia or electrolyte abnormalities prior to current admission, but an earlier test result compatible with primary hypothyroidism. The patient was diagnosed with autoimmune polyglandular syndrome type II (APS II). Clinical and laboratory findings improved after starting appropriate hormone replacement therapies along with insulin.

Conclusions: Evidence mostly obtained from case reports suggests that COVID-19 may induce a variety of autoimmune disorders in susceptible subjects. In our case, COVID-19 might have simply precipitated T1D and adrenal crisis in whom autoimmune thyroiditis may have been the first manifestation of an undiagnosed APS II. Or, COVID-19 may have triggered autoimmunity in the patient who was possibly predisposed to autoimmune disorders, and led to the development of APS II. Anyhow, more research is required to evaluate the possible link between COVID-19 and autoimmune disorders.

Introduction

Coronavirus Disease 2019 (COVID-19) emerged in Wuhan, China in late 2019; which was declared a pandemic by The World Health Organization in March 2020. Patients with COVID-19 may present with a variety of clinical symptoms, ranging from asymptomatic disease to acute respiratory distress syndrome and cytokine storm, and even death secondary to respiratory insufficiency, multi-organ failure or thrombotic events [1].

COVID-19, particularly when severe, is a hyperinflammatory disorder that might be linked to the development of autoimmune and/or autoinflammatory dysregulation in predisposed individuals [2]. Also, SARS-CoV-2, like numerous other viruses, may induce autoimmunity by molecular mimicry or by other ways [3]. Although a definitive relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the development of autoimmune and autoinflammatory disorders has yet to be proven, various autoimmune disorders that occur simultaneously or subsequent to COVID-19 have been described in case reports involving both adult and juvenile patients [4–7], including autoimmune type 1 diabetes (T1D) [8, 9]. To date, no cases of new-onset Addison's disease or autoimmune polyglandular syndrome type II (APS II) have been reported. Here we report and discuss the co-occurrence of new-onset

autoimmune T1D and Addison's disease in a patient who had mild COVID-19, and was also diagnosed with autoimmune thyroiditis, thus with APS II.

Case Presentation

A 60-year-old male presented with extreme fatigue, dyspnea and weight loss three weeks after testing positive for COVID-19 with a Polymerase Chain Reaction (PCR) test from nasopharyngeal swab material. He reported having anosmia, fatigue and dizziness at the time of PCR test positivity, but denied having fever, cough or dyspnea. He received five days of favipiravir treatment, and did not require hospitalization afterwards. His first hospital admittance with symptoms starting three weeks after PCR test positivity was to another center, during which a thorax computed tomography (CT) scan ruled out COVID-19 pneumonia, and initial laboratory testing showed no signs of severe COVID-19, such as leukopenia or increased D-dimer levels (Table 1, initial tests). However, due to elevated random plasma glucose level of 13.9 mmol/L (251 mg/dL) and severe hyponatremia, the patient was referred to our Endocrinology outpatient clinic.

Table 1
Laboratory examination of the patient.

	Normal Range	Initial tests*	Endocrinology Outpatient Clinic	
			First visit	2 months later
FPG (mmol/L)	3.3-5.5	13.9	13.6	
HbA1c (%)	3.5-5.6		12.5	9.1
BUN (mg/dL)	8-23	26.5	21.2	19.2
Creatinine (mg/dL)	0.6-1.2	1.2	1.0	0.9
Na (mEq/L)	136-146	112	121	132
Spot Urine Na (mEq/L)	<20	NA	92	
K (mEq/L)	3.5-5.1	NA	6.1	4.7
Ca (mg/dL)	8.8-10.6	9.3	9.9	10.3
P (mg/dL)	2.5-4.5	NA	4.5	4.9
Albumin (g/dL)	3.5-5.2	NA	4.3	4.7
ALT (U/L)	<50	69	54	50
AST (U/L)	<50	21	31	
GGT (U/L)	<55	NA	53	
ALP (U/L)	30-120	NA	78	
WBC ($x10^3$/μL)	4.3-10.3	11		
Neutrophil ($x10^3$/μL)	2.1-6.1	4,9		
Lymphocyte ($x10^3$/μL)	1.3-3.5	4.8		
Hb (g/dL)	13.6-17.2	17.5		
PLT ($x10^3$/μL)	156-373	546		
ACTH (pmol/L)	1.3-10.9		201	143.8
Cortisol (nmol/L)	184.8-623.4		222.6	
Renin (pmol/L)	0.03-0.3		>10.9	
Aldosterone (nmol/L)	97.1-832.3		0.1	
TSH (mIU/mL)	0.4-5.3	34.3	26.9	5.9

	Normal Range	Initial tests*	Endocrinology Outpatient Clinic	
			First visit	2 months later
fT4 (pmol/L)	7.8-14.4		11.71	
fT3 (pmol/L)	3.8-6		5.58	
AntiTPO (IU/mL)	0-9		743.6	
AntiTg (IU/mL)	0-4		33.6	
D-dimer (ng/mL)	<500	81.8		
CRP (mg/dL)	0-5	6		

FPG: Fasting blood glucose; HbA1c: Glycated hemoglobin; BUN: Blood urea nitrogen; Na: Sodium; K: Potassium; Ca: Calcium; P: Phosphorus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gama-glutamyl transferase; ALP: Alkaline phosphatase; WBC: White blood cell; PLT: Platelets; ACTH: Adrenocorticotrophic hormone; TSH: Thyroid stimulating hormone; fT4: Free tetraiodothyronine; fT3: Free triiodothyronine; AntiTPO: Thyroid peroxidase antibody; AntiTg: Thyroglobulin antibody; CRP: C-reactive protein; NA: Not available. *Initial laboratory tests were performed in another center.

At the time of his admission to our clinic, patient anamnesis revealed that he had lost 13 kg of body weight in the last three weeks and that he had recently begun to have difficulties even standing. He had anorexia but denied having abdominal pain, nausea or vomiting. Except for stage 1 hypertension which was not treated with medication, he had no previous medical history of chronic diseases. In his family history, type 2 diabetes (T2D) was found in the mother and three of five siblings, and hypertension was found in the father who deceased because of an ischemic stroke. He did not have any relatives with T1D or other autoimmune disorders. The patient was overweight with a body mass index of 27.04 kg/m^2 (31.44 kg/m^2 before weight loss). His blood pressure was 105/70 mmHg with a regular pulse of 112 beats per minute. There were no additional remarkable physical findings. A timeline is provided to help illustrate the progression of the case (Figure 1).

Laboratory test results of the patient are presented in Table 1. While having a high fasting plasma glucose level, urine analysis was negative for ketones. The patient had no clinical symptoms or signs compatible with acute pancreatitis, and abdominal CT scan revealed a normal-appearing pancreas gland. The patient was put on a low-dose basal insulin regimen (insulin glargine 12 U daily), and diagnosed with new-onset autoimmune T1D because the results came back positive for serum glutamic acid decarboxylase (GAD-65) antibodies (>2000 IU/mL, normal range: 0-10, enzyme immunoassay method). The patient did not show any neurological manifestations compatible with stiff-person syndrome.

Adrenal insufficiency, on the other hand, was also evaluated as a preliminary diagnosis in the patient due to extreme fatigue, weight loss, and severe electrolyte imbalances (Table 1). Serum adrenocorticotropic

hormone (ACTH) and cortisol levels were 201 pmol/L and 222.6 nmol/L, respectively. Serum levels of cortisol following intravenous administration of 250 mcg tetracosactid were 237.2 nmol/L at baseline, while 254.5 and 242.7 nmol/L at 30th and 60th minutes, showing a lack of responsiveness to ACTH stimulation. Plasma renin and aldosterone levels were >10.9 pmol/L (normal range, 0.03-0.3) and 0.1 nmol/L (normal range, 0.09-0.8), respectively. The adrenal glands appeared normal in CT scan (Figure 2). A diagnosis of primary adrenal insufficiency was made based on the clinical and laboratory findings, and the patient was started on 15 mg of oral prednisone daily which dramatically improved his symptoms. In order to determine the etiology of primary adrenal insufficiency in the patient with new-onset autoimmune T1D, a serum test for antibodies to the adrenal cortex (indirect immunofluorescence assay, reagent: NOVA Lite® Monkey Ovary Testis Adrenal IFA Slides, Cerba Laboratories, France) was ordered which came back positive as 160 (reference value, <5). Fludrocortisone was started at a dose of 0.1 mg/day when prednisone was lowered to 7.5 mg/day.

The patient also had hypothyroidism due to autoimmune thyroiditis, as evidenced by elevated TSH levels of 34.3 and 26.9 mIU/L on two separate occasions and positive anti-thyroid peroxidase and anti-thyroglobulin antibodies (Table 1). His free T4 and free T3 levels were in normal range. Levothyroxine replacement (50 mcg daily) was started five days after the initiation of oral prednisone. When reviewing the patient's former medical records, we discovered an earlier test result (year 2018, TSH: 57.13 mIU/mL, fT4: 9.13 pmol/L, fT3: 3.5 pmol/L) consistent with primary hypothyroidism without antibody testing, however, there was no evidence of previous increased plasma glucose levels or electrolyte imbalance in his medical records. We have checked the patient for celiac disease-specific antibodies, all of which were negative. Although we were unable to test the patient for anti-pituitary antibodies, all anterior pituitary hormone levels were within normal limits, and he showed no clinical or laboratory signs of diabetes insipidus.

The patient was well after two months of treatment with prednisone, fludrocortisone, and levothyroxine replacements in appropriate doses. His blood pressure was 145/100 mmHg, possibly reflecting his previous stage I hypertensive state prior to COVID-19. Table 1 shows the laboratory evaluation on follow-up. Self-measured blood sugar levels at 7 points were within targets, and HbA1c was reduced by approximately 3%.

Discussion

Here we have described a 60-year-old male patient with new-onset T1D and primary adrenal insufficiency, both of which were associated with high titers of disease-specific autoantibodies, and jointly manifested with an abrupt and robust onset three weeks following PCR test positivity for COVID-19. The course of COVID-19 in the patient was mild without pulmonary involvement or laboratory signs of severe disease. Our patient also had hypothyroidism due to autoimmune thyroiditis, which he may probably have for several years since we have discovered a former test result compatible with primary hypothyroidism; however, prior laboratory data up on the thyroid autoantibodies were unavailable. To the best of our

knowledge, this is the first reported case of new-onset autoimmune T1D and new-onset autoimmune adrenal insufficiency (Addison's disease) co-occurring in an individual patient with COVID-19.

New-onset diabetes has been reported in an increasing number of cases with COVID-19 [8–17], however, it is unclear whether there is a true link between COVID-19 and new-onset T1D. Although various cohorts reported increased number of children presenting with diabetic ketoacidosis (DKA) during the pandemic [18–21], it may reflect patients attempting to delay hospital admission due to their fear of being infected with SARS-CoV-2, since the rate of new-onset T1D was not far from that estimated [22]. As to the adult population, the prevalence of new-onset T1D was reported to be 9.8% among a small cohort of adolescents and young adults with confirmed or suspected COVID-19 [23]. In fact, the type of new-onset diabetes in the course of COVID-19 has usually been determined based on parameters such as patient age, absence or presence of risk factors for T2D such as obesity, prediabetes, family history, etc. Autoantibodies were not always examined despite the presence of DKA [11, 12, 14–16]. GAD-65, islet cell, and insulin antibodies, on the other hand, were all negative in certain patients with COVID-19 presenting with DKA [13, 17]. Exceptionally, even though our case did not present with DKA, he had remarkably high titers of GAD-65 antibodies at the time of diabetes diagnosis, and despite having certain risk factors for T2D such as older age and a strong family history, he was diagnosed with T1D. A case similar to ours, but involving a younger patient (29-year-old woman) who had previously undergone bariatric surgery, was reported. Four weeks after testing positive for COVID-19, the patient had new-onset diabetes without ketoacidosis, and GAD-65 antibody was positive. Both type 1 and type 2 diabetes were present in the family history, yet no additional autoimmune disorders were mentioned in the patient [8]. In another case of 32-year-old male presenting with COVID-19 pneumonia and DKA, GAD and zinc transporter 8 antibodies were both positive, although no further information on family history or metabolic risk factors was provided [9].

SARS-CoV-2 infects humans by binding to the cellular Angiotensin-converting enzyme 2 (ACE2) receptor [24]. ACE2 expression has been found in a wide range of human tissues, including the pancreas [25]. According to autopsy studies, SARS-CoV-2 can infect and damage pancreatic beta cells [26–28], which could be one, but not the only, underlying cause of development of DKA as well as new-onset diabetes in patients with COVID-19. Proinflammatory state causing insulin resistance, and decreased insulin delivery to tissues as a result of endothelial dysfunction could be counted among the probable links between COVID-19 and diabetes, as well as triggered autoimmunity [29, 30]. It is well-known that several viruses, including cytomegalovirus, Epstein-Barr virus, rotavirus and especially coxsackievirus, have been implicated in the autoimmune processes that lead to T1D [31–34]. Molecular mimicry between viral and human proteins, immunologic cross-reactivity with autoantigens, and bystander activation of autoreactive T cells are among proposed mechanisms for the role of viruses in the pathogenesis of T1D [35]. In combination with immune system hyperstimulation, SARS-CoV-2 appears be capable of triggering autoimmunity in subjects who are prone to autoimmune disorders by utilizing similar processes [36]. For example, one might speculate that release of self-antigens as a consequence of SARS-CoV-2-induced beta cell damage, and presentation of these antigens to pre-existing autoreactive T cells might accelerate T1D onset, as this is considered as one of the possible mechanisms by which viruses trigger T1D in

susceptible individuals [35]. For the time being, the data from studies looking into the relationship between COVID-19 and diabetes are insufficient to shed light on the role of autoimmunity.

Primary adrenal insufficiency in patients infected with SARS-CoV-2 has been reported less frequently, all of which (n=6 confirmed cases) were associated with hemorrhagic or non-hemorrhagic infarction of adrenal glands [37]. In fact, autopsy studies [38, 39] and a retrospective analysis of computed tomography examinations in severe COVID-19 patients [40] revealed that inflammatory and/or hemorrhagic changes in the adrenal glands are not uncommon in patients with severe COVID-19. These findings are consistent with the thrombo-inflammatory nature of COVID-19. While no other cases of COVID-19 related Addison's disease have been reported to date, two reported cases of COVID-19 associated bilateral adrenal hemorrhage were diagnosed with primary antiphospholipid syndrome, one of whom had an additional autoimmune disease (autoimmune hepatitis) [37, 41]. However, both patients with COVID-19 associated bilateral adrenal hemorrhage appeared to have undiagnosed antiphospholipid syndrome prior to COVID-19 [37, 41]. The normal appearing adrenal glands, positive antibodies to the adrenal cortex, and co-existence of T1D and autoimmune thyroiditis in our patient, in whom SARS-CoV-2 infection was the most likely precipitating factor for the occurrence of acute adrenal crisis, suggest that he might possibly have previously undiagnosed APS II. However, while the most common presentation of APS II is as adrenal insufficiency and T1D [42], hypothyroidism was the first manifestation of the syndrome in our patient. Besides, it is not common for adrenal insufficiency to emerge in 6th decade of life in patients with APS II [42]. Furthermore, although development of adrenal insufficiency in Addison's disease is usually gradual [43], our patient had no prior symptoms or laboratory records in support of progressing adrenal insufficiency such as progressive fatigue or electrolyte abnormalities. In addition, because he was not being treated for his hypothyroidism, if he had a gradual disease course, one can expect that symptoms of adrenal insufficiency to be more evident, and he would have been diagnosed earlier. Also, very high levels of both GAD-65 antibody and antibodies to the adrenal cortex might imply that both T1D and Addison's disease in our case have an acute onset.

COVID-19 related APS II has never been reported in the literature to date. However, there have been reports of patients in whom APS II was precipitated by EBV [44] and Influenza [45] infections. The presentation of the latter patient was quite similar to ours: adrenal crisis was induced by Influenza infection in a 57-year-old female patient with known autoimmune thyroiditis; however, unlike our patient, some symptoms and findings of adrenal insufficiency had gradually developed over the previous year [45]. Because the autoantibody status of our case was unknown prior to COVID-19, and we did not screen for human leukocyte antigen (HLA) haplotypes that confer the risk of having multiple autoimmune disorders [43], it was impossible to make a definitive judgment whether the patient had unrecognized APS II or not. Nevertheless, SARS-CoV-2 infection appears to be the triggering factor that accelerated, if not initiated, the occurrence of T1D and Addison's disease in our patient.

Conclusion

We have described, for the first time, the co-occurrence of new-onset autoimmune T1D and Addison's disease in a patient with mild COVID-19. Because the patient also had hypothyroidism due to autoimmune thyroiditis, and he had a former test result consistent with primary hypothyroidism, it is reasonable to assume that hypothyroidism was the first manifestation of an undiagnosed APS II, and SARS-CoV-2 infection precipitated T1D and adrenal crisis, just as several viral infections can. COVID-19, on the other hand, may have played a distinctive role in inducing autoimmunity and the development of APS II in this patient. Despite several case reports indicating a possible link between COVID-19 and new-onset autoimmune diseases, and while some evidence suggests that SARS-CoV-2 may cause autoimmunity in susceptible subjects, more research is still required.

Declarations

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The authors declare that they have no conflict of interest.

Informed consent:

Informed consent has been obtained from the patient for publication of the case report and accompanying images.

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Figures

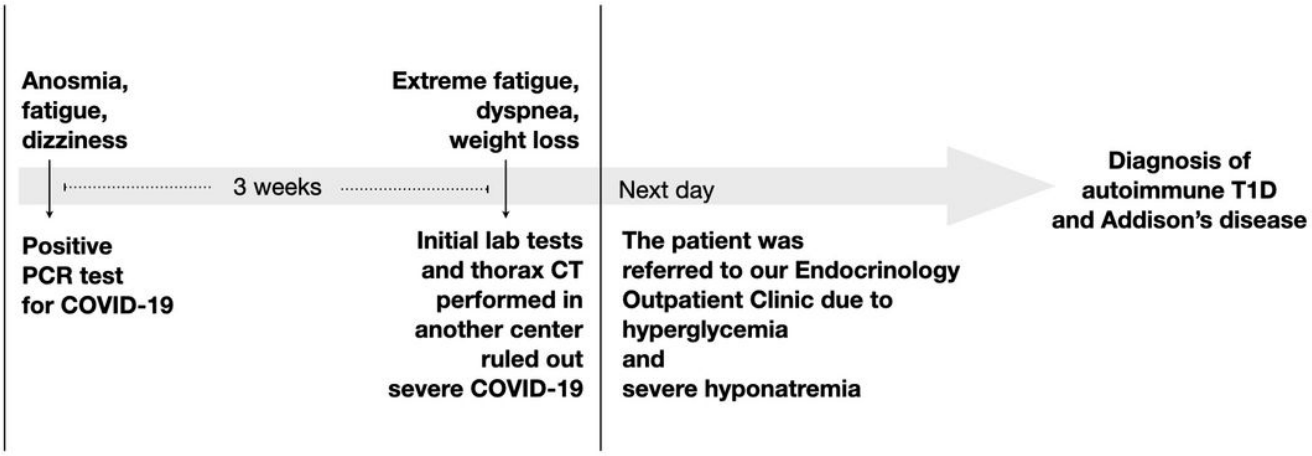

Figure 1

Timeline illustrating the progression of the case.

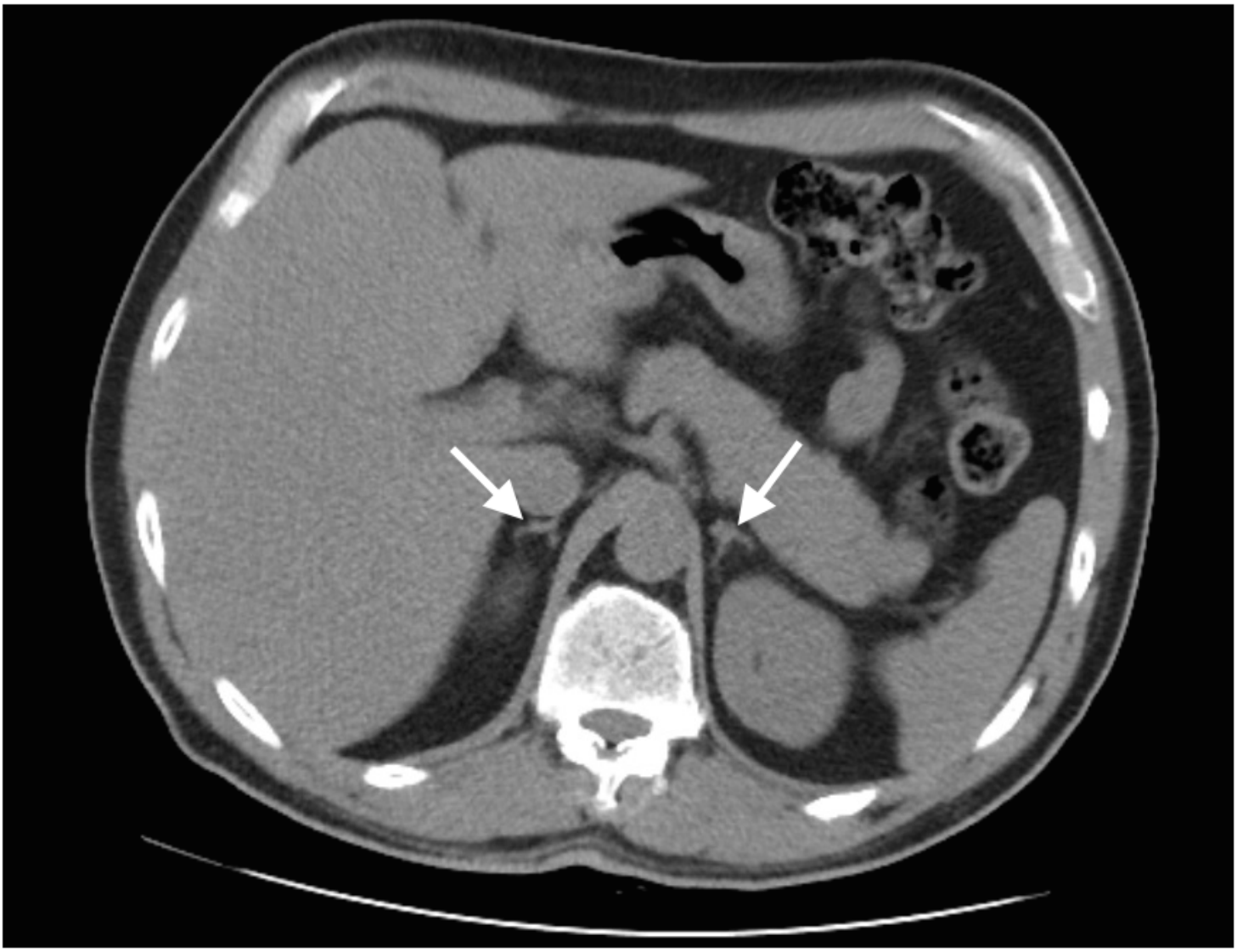

Figure 2

Computed tomography image of the patient revealing normal appearing adrenal glands (arrows).