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CASE REPORT
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Emergence of Autoimmune Type 1 Diabetes and Acute Adrenal Crisis Following Coronavirus Disease 2019

ABSTRACT

A 60-year-old male presented with extreme fatigue and weight loss 3 weeks after testing positive for coronavirus disease 2019. The course of coronavirus disease 2019 was mild, without pulmonary involvement. The patient showed symptoms and laboratory signs of new-onset diabetes without ketoacidosis and acute primary adrenal insufficiency, the latter of which was confirmed with an adrenocorticotrophic hormone stimulation test. Glutamic acid decarboxylase-65 antibody and antibodies to the adrenal cortex were positive in high titers. Previous medical records of the patient revealed no hyperglycemia or electrolyte abnormalities prior to current admission, but an earlier test result was compatible with primary hypothyroidism which was associated with autoimmune thyroiditis. He was therefore diagnosed with autoimmune polyglandular syndrome type II. Clinical and laboratory findings improved after starting appropriate hormone replacement therapies along with insulin. Coronavirus disease 2019 may induce a variety of autoimmune disorders in susceptible subjects. In our case, coronavirus disease 2019 might have simply precipitated type 1 diabetes and adrenal insufficiency in whom autoimmune thyroiditis may have been the first manifestation of an undiagnosed autoimmune polyglandular syndrome type II. Coronavirus disease 2019 might have triggered autoimmunity in the patient who was possibly predisposed to autoimmune disorders. Anyhow, more research is required to evaluate the possible link between coronavirus disease 2019 and autoimmune disorders.

Keywords: Coronavirus disease 2019, autoimmune polyglandular syndrome, adrenal insufficiency, Addison's disease, type 1 diabetes

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been supposed to trigger autoimmune diseases in predisposed individuals through molecular mimicry, immune dysregulation, or yet-to-be-discovered mechanisms.[1] Although a definitive relationship between SARS-CoV-2 and the development of autoimmune disorders has yet to be proven, various autoimmune disorders that occur simultaneously or subsequent to COVID-19 have been described involving both adult and juvenile patients,[2,3] including autoimmune type 1 diabetes (T1D)[4,5] and autoimmune adrenal insufficiency (AI).[6] To date, no cases with autoimmune polyglandular syndrome type II (APS II) have been reported.

Case Presentation

A 60-year-old male presented with extreme fatigue, dyspnea, and weight loss 3 weeks after testing positive for coronavirus disease 2019 (COVID-19) with a polymerase chain reaction (PCR) test from nasopharyngeal swab material. He had anosmia, fatigue, and dizziness at the time of PCR test positivity but denied having fever, cough, or dyspnea. He received 5 days of favipiravir treatment (used to be the first-line medical treatment) and did not require hospitalization.

The first hospital admittance with his symptoms starting 3 weeks after PCR test positivity was to another center, during which a thorax computed tomography (CT) scan ruled out COVID-19 pneumonia. Laboratory tests showed no signs of severe COVID-19 (Table 1, initial tests) but elevated levels of random plasma glucose and severe hyponatremia. The patient was referred to our endocrinology outpatient clinic.

Patient's anamnesis revealed that he had lost 13 kg of body weight in the last 3 weeks and that he had recently begun to have difficulties even standing. He had anorexia but denied

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having abdominal pain, nausea, or vomiting. Except for hypertension (no anti-hypertensive medication), he had no previous medical history. Type 2 diabetes (T2D) was found in the mother and 3 of 5 siblings. His family history was negative for autoimmune disorders. The patient was unwell, with a blood pressure of 105/70 mmHg and a regular pulse of 112 beats per minute. His body mass index was 27.04 kg/m^2 (31.44 kg/m^2 before weight loss). Physical findings were otherwise normal. A timeline is provided to help illustrate the progression of the case (Figure 1).

Laboratory results of the patient are presented in Table 1. While having a high fasting plasma glucose level, urine analysis was negative for ketones. He had no clinical symptoms or signs compatible with acute pancreatitis, and an abdominal CT scan revealed a normal-appearing pancreas. The patient was put on subcutaneous insulin and diagnosed with new-onset T1D with extremely high glutamic acid decarboxylase (GAD-65) antibodies (>2000 IU/mL, normal range: 0-10, enzyme immunoassay method).

Meanwhile, plasma adrenocorticotropic hormone (ACTH) and cortisol levels were 201 pmol/L and 222.6 nmol/L, respectively. Cortisol responses 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, indicating a lack of responsiveness. The adrenal glands appeared normal in the CT scan (Figure 2). Oral prednisone 15 mg/day was started, which dramatically improved the symptoms. Antibodies to the adrenal cortex (indirect immunofluorescence assay, reagent: NOVA Lite® Monkey Ovary–Testis–Adrenal IFA Slides, Cerba Laboratories, France) were found positive (160; reference value <5). Fludrocortisone was started at a dose of 0.1 mg/day when prednisone was lowered to 7.5 mg/day.

Also, the patient had elevated TSH levels of 34.3 and 26.9 mIU/L on 2 separate occasions and positive anti-thyroid peroxidase and anti-thyroglobulin antibodies (Table 1). Levothyroxine replacement (50 mcg daily) was started 5 days after the initiation of glucocorticoids. While 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. No evidence of increased plasma glucose or electrolyte imbalance was found. We checked for celiac disease-specific antibodies, but all came negative. We were unable to test for anti-pituitary antibodies, but all anterior pituitary hormone levels were within normal limits. He showed no clinical or laboratory signs of diabetes insipidus.

Table 1. Laboratory Test Results

			Endocrinology Outpatient Clinic	
	Normal Range	Initial Tests*	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	N/A	92	
K (mEq/L)	3.5-5.1	N/A	6.1	4.7
Ca (mg/dL)	8.8-10.6	9.3	9.9	10.3
P (mg/dL)	2.5-4.5	N/A	4.5	4.9
Albumin (g/dL)	3.5-5.2	N/A	4.3	4.7
ALT (U/L)	<50	69	54	50
AST (U/L)	<50	21	31	
GGT (U/L)	<55	N/A	53	
ALP (U/L)	30-120	N/A	78	
WBC (×10^3/μL)	4.3-10.3	11		
Neutrophil (×10^3/μL)	2.1-6.1	4.9		
Lymphocyte (×10^3/μL)	1.3-3.5	4.8		
Hb (g/dL)	13.6-17.2	17.5		
PLT (×10^3/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
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		

*Initial laboratory tests were performed in another center.
ACTH, adrenocorticotrophic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AntiTg, thyroglobulin antibody; AntiTPO, thyroid peroxidase antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; CRP, C-reactive protein; FPG, fasting blood glucose; fT3, rree triiodothyronine; fT4, free tetraiodothyronine; GGT, gama-glutamyl transferase; HbA1c, glycated hemoglobin; K, potassium; Na, sodium; NA, not available; P, phosphorus; PLT, platelets; TSH, thyroid-stimulating hormone; WBC, white blood cell.

MAIN POINTS

- We have reported the co-occurrence of new-onset autoimmune type 1 diabetes and Addison's disease following mild coronavirus disease 2019 (COVID-19). Given the co-existence of autoimmune thyroiditis, the patient was diagnosed with autoimmune polyglandular syndrome type II (APS II).
- Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may supposedly trigger autoimmune diseases in predisposed individuals. Numerous case reports of various autoimmune disorders have been published in the literature, but APS II is first.
- Further studies are needed to support the hypotheses that SARS-CoV-2 might induce autoimmunity in susceptible individuals. Long-term follow-up of patients with COVID-19-associated autoimmune diseases is required.

He was well after a 2-month treatment with insulin, prednisone, fludrocortisone, and levothyroxine with appropriate doses. Table 1 shows the laboratory evaluation on follow-up. Self-measured 7-point capillary glucose levels were within targets, and HbA1c was reduced by approximately 3%.

Informed Consent

Informed consent has been obtained from the patient for the publication of the case report and accompanying images. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional

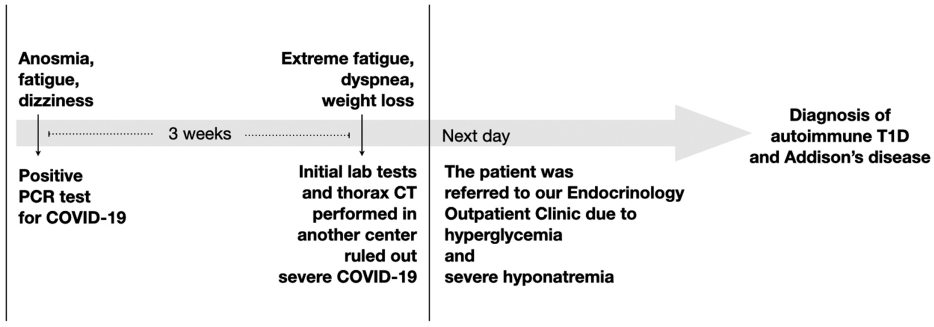

Figure 1. Timeline illustrating the progression of the case.

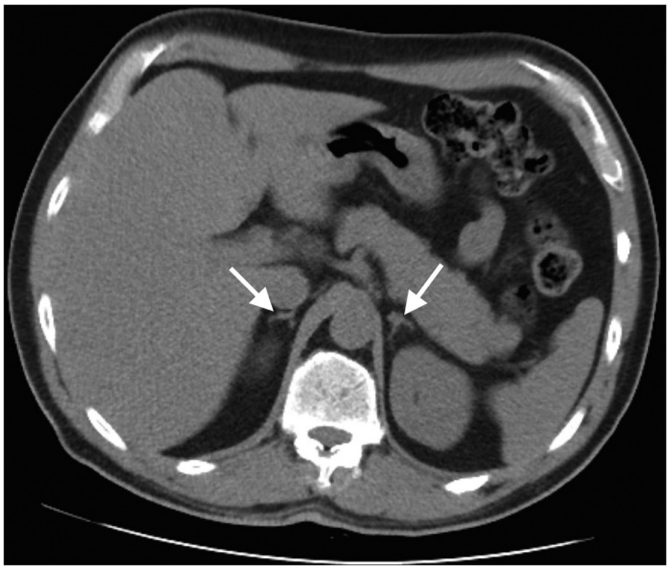

Figure 2. Computed tomography image of the patient revealing normal appearing adrenal glands (arrows).

and national) and/or with the Helsinki Declaration of 1964 and later versions.

Discussion

New-onset diabetes associated with COVID-19 has been described in a number of studies[7,8] and case reports.[4,5,9-13] Currently, it is unknown whether there is a direct relationship between COVID-19 and new-onset diabetes, particularly T1D.[14] Severe acute respiratory syndrome coronavirus-2 may enter a wide range of human tissues, including the pancreas, by binding to the cellular angiotensin-converting enzyme 2 receptor.[15] Severe acute respiratory syndrome coronavirus-2, therefore, may infect and damage pancreatic beta cells,[16] which could be one but not the sole underlying cause of DKA as well as new-onset diabetes in COVID-19. A proinflammatory state causing insulin resistance and decreased insulin delivery to tissues as a result of endothelial dysfunction and hypoxia could be accounted for the probable links between COVID-19 and diabetes as well as triggered autoimmunity in susceptible subjects.[17] It is well known that several viruses, including cytomegalovirus, Epstein–Barr virus (EBV), rotavirus, and, in particular, coxsackievirus have been implicated in the autoimmune processes that lead to T1D.[18,19] Molecular mimicry between viral and human proteins, immunologic cross-reactivity with autoantigens, and bystander activation of autoreactive T cells are among the proposed mechanisms for the role of viruses in the pathogenesis of T1D.[20] Release of self-antigens as a consequence of SARS-CoV-2-induced beta cell damage, and presentation of these antigens to preexisting 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.[20]

The type of new-onset diabetes in the course of COVID-19 has usually been determined based on parameters such as age and absence or presence of risk factors for T2D such as obesity, prediabetes, and family history. Autoantibodies have not been always examined despite the presence of DKA.[9,11,12] Glutamic acid decarboxylase-65, islet cell, and insulin antibodies, on the other hand, were all negative in certain patients with COVID-19 presenting with DKA.[10,13] Despite not having DKA and even having risk factors for type 2 diabetes such as advanced age, obesity, and a significant family background, our patient had elevated GAD-65 antibody titers at the time of diabetes diagnosis. Furthermore, no signs of prediabetes were found in earlier medical documents, supporting the abrupt onset of hyperglycemia rather than a gradual development of diabetes. Regrettably, serum c-peptide and insulin levels were not measured. A similar case of a 29-year-old woman who had previously undergone bariatric surgery has been reported.[7] Four weeks after testing positive for COVID-19, the patient had new-onset diabetes without ketoacidosis, and GAD-65 antibody was positive.[7] Both type 1 and type 2 diabetes were present in her family history, yet no additional autoimmune disorders have been mentioned.[4]

Primary AI in patients with SARS-CoV-2 has been reported less frequently, most of which were associated with hemorrhagic or non-hemorrhagic infarction of adrenal glands.[21] Adrenal glands of our patient, however, appeared normal on CT, ruling out hemorrhage, infarction, and infiltrative diseases. There has been only one other report of a patient presenting with autoimmune AI, occurring 5 months after asymptomatic COVID-19. The patient was a 64-year-old woman with a history of T2D and hypothyroidism. She had normal-appearing adrenal glands and positive antibodies to the adrenal cortex similar to our patient, but no additional autoimmune disorders were identified.[6] Our patient had concurrent T1D and autoimmune thyroiditis, implying that he might possibly have previously undiagnosed APS II. However, while the most common presentation of APS II is as AI and T1D,[22] hypothyroidism was the first manifestation of the syndrome in our patient. Besides, it is not common for AI to emerge in the sixth decade of life in patients with APS II. Furthermore, although the development of AI in Addison's disease is usually gradual,[22] our patient had no previous signs or laboratory data indicating that AI

was already gradually developing before COVID-19, such as fatigue, anorexia, or electrolyte imbalances, which led us to assume that autoimmune AI emerged concurrently with T1D.

Coronavirus disease 2019-related APS II has never been reported in the literature till now. However, there have been reports of patients in whom APS II was precipitated by EBV[23] and Influenza[24] infections. The presentation of the latter patient was quite similar to ours: the adrenal crisis was induced by influenza infection in a 57-year-old female with known autoimmune thyroiditis; however, unlike our patient, some symptoms and findings of AI had gradually developed over the previous year.[24] Regrettably, the autoantibody status of our case was unknown prior to COVID-19, and we did not screen the patient for human leukocyte antigen (HLA) haplotypes that confer the risk of having multiple autoimmune disorders.[22]

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 AI. Severe acute respiratory syndrome coronavirus-2 might have played a role in inducing the manifestation of clinical APS II in this patient. Further studies are needed to support the hypotheses that SARS-CoV-2 might induce autoimmunity in susceptible individuals. Also, long-term follow-up of patients with COVID-19-associated autoimmune diseases is required to gain more insight.

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

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Declaration of Interests: The authors have no conflict of interest to declare.

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References

1. Dotan A, Muller S, Kanduc D, David P, Halpert G, Shoenfeld Y. The SARS-CoV-2 as an instrumental trigger of autoimmunity. *Autoimmun Rev*. 2021;20(4):102792. [CrossRef]
2. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-1778. [CrossRef]
3. Toscano G, Palmerini F, Ravaglia S, et al. Guillain-barre syndrome associated with SARS-CoV-2. *N Engl J Med*. 2020;382(26):2574-2576. [CrossRef]
4. Marchand L, Pecquet M, Luyton C. Type 1 diabetes onset triggered by COVID-19. *Acta Diabetol*. 2020;57(10):1265-1266. [CrossRef]
5. Potier L, Julla JB, Roussel R, et al. COVID-19 symptoms masking inaugural ketoacidosis of type 1 diabetes. *Diabetes Metab*. 2021;47(1):101162. [CrossRef]
6. Sánchez J, Cohen M, Zapater JL, Eisenberg Y. Primary adrenal insufficiency after COVID-19 infection. *AACE Clin Case Rep*. 2022;8(2):51-53. [CrossRef]
7. Li H, Tian S, Chen T, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes Obes Metab*. 2020;22(10):1897-1906. [CrossRef]
8. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2021;23(3):870-874. [CrossRef]
9. Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: causality or coincidence? A report of three cases. *J Med Virol*. 2021;93(2):1150-1153. [CrossRef]
10. Hollstein T, Schulte DM, Schulz J, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. *Nat Metab*. 2020;2(10):1021-1024. [CrossRef]
11. Heaney AI, Griffin GD, Simon EL. Newly diagnosed diabetes and diabetic ketoacidosis precipitated by COVID-19 infection. *Am J Emerg Med*. 2020;38(11):2491.e3-2491.e4. [CrossRef]
12. Ghosh A, Misra A. Marked hyperglycemia and ketosis in a non-obese patient with new onset diabetes and very mild COVID-19 symptoms: a case report. *Diabetes Metab Syndr*. 2021;15(1):213-214. [CrossRef]
13. Palermo NE, Sadhu AR, McDonnell ME. Diabetic ketoacidosis in COVID-19: unique concerns and considerations. *J Clin Endocrinol Metab*. 2020;105(8). [CrossRef]
14. Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, hyperglycemia, and new-onset diabetes. *Diabetes Care*. 2021;44(12):2645-2655. [CrossRef]
15. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 Receptor and Regulator of the renin-angiotensin System: celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res*. 2020;126(10):1456-1474. [CrossRef]
16. Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab*. 2021;3(2):149-165. [CrossRef]
17. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol*. 2021;17(1):11-30. [CrossRef]
18. Hober D, Sauter P. Pathogenesis of type 1 diabetes mellitus: interplay between enterovirus and host. *Nat Rev Endocrinol*. 2010;6(5):279-289. [CrossRef]
19. Ghazarian L, Diana J, Simoni Y, Beaudoin L, Lehuen A. Prevention or acceleration of type 1 diabetes by viruses. *Cell Mol Life Sci*. 2013;70(2):239-255. [CrossRef]
20. Pane JA, Coulson BS. Lessons from the mouse: potential contribution of bystander lymphocyte activation by viruses to human type 1 diabetes. *Diabetologia*. 2015;58(6):1149-1159. [CrossRef]
21. Machado IFR, Menezes IQ, Figueiredo SR, et al. Primary adrenal insufficiency due to bilateral adrenal infarction in COVID-19: a case report. *J Clin Endocrinol Metab*. 2022;107(1):e394–e400. [CrossRef]
22. Michels AW, Gottlieb PA. Autoimmune polyglandular syndromes. *Nat Rev Endocrinol*. 2010;6(5):270-277. [CrossRef]
23. Roa A, Lew L, DiJohn D. Polyglandular syndrome type II in association with Epstein-Barr virus: a case report. *Clin Pediatr (Phila)*. 2008;47(6):604-606. [CrossRef]
24. Bain A, Stewart M, Mwamure P, Nirmalaraj K. Addison's disease in a patient with hypothyroidism: autoimmune polyglandular syndrome type 2. *BMJ Case Rep*. 2015;2015. [CrossRef]