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Case Report

SARS-CoV-2-Induced Adrenal Crisis in a Patient with Autoimmune Polyglandular Syndrome Type 1: Case Report

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Abstract

Autoimmune polyglandular syndromes (APS) are rare disorders characterized by the coexistence of endocrine and non-endocrine dysfunctions mediated by autoimmune mechanisms. Autoimmune polyglandular syndrome type 1 is defined as coexistence of chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency. Addison's disease as the obligatory component is potentially life threatening.

Herein, we demonstrate a case of a 44-year-old woman with APS-1 (hypoparathyroidism, adrenal insufficiency, hypergonadotropic hypogonadism) and SARS-CoV-2-induced adrenal crisis. The patient presented with the typical manifestations of hypotensive shock, electrolyte disturbances of hyponatremia and hyperkalemia, and hypoglycaemia.

Our case report illustrates the increased risk of severe course of COVID-19 in APS-1 syndrome patients along with heightened exposure to medical complications. The case reinforced the significance of a timely diagnosis, appropriate treatment, and education of patients with such a rare condition like APS-1.

Keywords

adrenal crisis, APS-1, COVID-19

INTRODUCTION

Autoimmune polyglandular syndromes (APS) are rare disorders characterized by the coexistence of endocrine and non-endocrine dysfunctions mediated by autoimmune mechanisms.[1] APS are mainly classified into 4 types: type 1 (the presence of at least 2 of chronic candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency), type 2 (autoimmune adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes mellitus), type 3 (autoimmune thyroid disease with other autoimmune diseases, excluding chronic candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency), and type 4 (2 or more organ-specific autoimmune diseases that do not fall into types 1, 2, or 3).[2] The spectrum of autoimmune disorders varies among different types, but type 1 and type 2 include hypoglucocorticism as an obligatory component.

Autoimmune polyglandular syndrome type 1 (APS-1) is defined as the presence of two or more of the following: adrenocortical insufficiency, chronic mucocutaneous candidiasis, and hypoparathyroidism.[3] It is a rare autosomal recessive disease caused by mutations in the autoimmune

regulator gene (AIRE).[4] The estimated prevalence is 1:80000 in most countries.[5] Besides the three aforementioned major features, other components of APS-1 include type 1 diabetes, autoimmune hepatitis, hypothyroidism, primary hypogonadism, pernicious anemia, alopecia, ectodermal dysplasia, malabsorption, and vitiligo.[6]

A life-threatening complication of the adrenal insufficiency is the adrenal crisis with a mortality rate reaching 0.5/100 patient-years.[7] The occurrence of this complication is most often triggered by concomitant infectious.[8]

Up to now, more than 117 million cases of SARS-CoV-2 infection have been reported worldwide. The course of coronavirus disease 19 (COVID-19) varies among the affected individuals, ranging from asymptomatic to acute respiratory distress syndrome (ARDS).[9,10] In severe cases, the initial immune response is followed by a pulmonary phase presenting with hyperinflammation and immunosuppression.

CASE REPORT

A 44-year-old woman positive for SARS-CoV-2 infection was referred to our COVID-19 unit in December 2020. She complained of fever, dry cough, sore throat, headache, fatigue, muscle ache, anorexia, nausea, and vomiting persisting for a week. The reason for the hospitalization was newly developed dyspnea and abdominal tenderness along with progressive worsening of her general health status.

The thorough history and medical documentation revealed concomitant autoimmune polyglandular syndrome type 1 – hypoparathyroidism, adrenal insufficiency, and hypergonadotropic hypogonadism. In 1982, at the age of 6, she was diagnosed with hypoparathyroidism that manifested with muscle weakness, paresthesias and tetanic seizures. Serum levels of calcium and PTH were low and she was started on replacement therapy with vitamin D derivatives and calcium supplement, which she currently takes. The investigations then showed calcifications of the basal ganglia, and bilateral symmetric cataract that was removed in 1986. In 1991, she was diagnosed with primary hypocorticism and started on replacement therapy with prednisone 5 mg and fludrocortisone 0.05 mg. She established menarche at the age of 12 and reported regular menstrual pattern until 2004, at the age of 28, when she reported oligomenorrhea. Then she was diagnosed with hypergonadotropic hypogonadism and was put on hormone replacement therapy with estradiol 2 mg and gestagen. In 2006, she experienced transient acute renal failure and was diagnosed with tubulointerstitial nephritis.

Family history was negative for inherent diseases.

Physical examination upon admission

The patient was somnolent, confused, subfebrile (temperature 37.5°C). She appeared pale, dehydrated with dry mucous membranes, and poor skin turgor. Asthenic habitus with BMI 17.73 kg/m^2. She was hypotensive with a blood pressure of 85/60 mmHg, rhythmic heartbeat, heart rate 110 bpm, and no heart murmurs. Vesicular breathing with mild crackles in the lung bases, respiratory rate of 22-24 breaths/min, finger oxygen saturation 85% in room air. There was a generalized abdominal tenderness, which was otherwise soft to palpation and showed no rebound.

The patient was consulted by neurologist and gynecologist who declined neurological or gynecological problem.

Imaging examinations

A chest X-ray was performed showing bilateral and peripheral opacities throughout the lung fields consistent with bilateral pneumonia. The ultrasound scan of the abdomen was unremarkable.

The electrocardiogram showed sinus tachycardia.

Reverse transcriptase real-time qualitative polymerase chain reaction (RT-PCR) for SARS-CoV-2 from oropharyngeal and nasopharyngeal swabs became positive.

Laboratory examinations

Laboratory examinations upon admission and during hospitalization are shown in ***Table 1***.

Differential diagnosis of APS

Diagnosis of APS is suggested clinically and confirmed by detecting deficient hormone levels. Other causes of multiple endocrine deficiencies include hypothalamic-pituitary dysfunction and coincidental endocrine dysfunction due to separate causes. Detecting autoantibodies to each affected glandular tissue can help differentiate APS from the other causes and verifies the autoimmune etiology of the disease, and elevated levels of pituitary tropic hormones suggest that the hypothalamic-pituitary axis is intact. At the time of her current hospitalization, other causes of endocrine deficiencies were excluded and the patient was already diagnosed with APS type 1 and was on replacement treatment. That is why we did not need to perform end-organ function and stimulating tests to confirm the diagnosis.

Treatment

The patient was initially managed with oxygen therapy with a face mask at 8-10 L/min, obtaining saturations of 96%. She received treatment with broad-spectrum antibiotics as follows: ampicillin/sulbactam 1.0/0.5 g IV BID for 7 days and levofloxacin 500 mg IV QD for 5 days. In addition, she was treated with intravenous ascorbic acid, vitamin B complex, famotidine 20 mg BID, calcitriol 0.25 mcg QD and 10% solution of calcium gluconate and 2 g of magnesium infusion according to calcium and magnesium serum concentrations. Thromboprophylaxis was started with 40 mg nadroparin BID given subcutaneously. Given concerns for adrenal crisis, dyspnea and the lack of hydrocortisone in our country, intra-

Table 1. Laboratory data of patient upon admission and during hospitalization

PARAMETER (REFERENCE RANGE)	Hospitalization Day				
	1	2	3	5	9
COMPLETE BLOOD COUNT					
Hematocrit (0.35-0.54%)	0.373		0.305	0.301	
Hemoglobin (110-160 g/L)	129		104	100.0	
Eritrocytes (3.5-5.5 $\times 10^{12}$/L)	4.37		3.53	3.42	
MCV (82-95 fl)	85.4		86.4	88.0	
MCH (27-32 pg)	29.6		29.4	29.1	
MCHC (320-360 g/L)	347		340.0	331.0	
RDW (11-16 %)	13.9		13.9		
White blood cell (3.5-10 $\times 10^9$/L)	23.23		18.62	6.72	
Granulocytes (50-70%)	95.5		89.0		
Lymphocytes (20-40%)	3.1		6.0		
Monocytes (3-10%)	0.7		4.4		
Eosinophils (0.5-6%)	0.2		0.1		
Basophils (0-1%)	0.5		0.5		
Granulocytes (2-7 $\times 10^9$/L)	22.19		16.58		
Lymphocytes (0.80-4 $\times 10^9$/L)	0.72		1.12		
Monocytes (0.112-1.2 $\times 10^9$/L)	0.16		0.81		
Eosinophils (0.02-0.5 $\times 10^9$/L)	0.05		0.02		
Basophils (0-0.10 $\times 10^9$/L)	0.11		0.09		
Platelets (140-400$\times 10^9$/L)	339.0		440.0	523.0	
MPV (6.5-12 fl)	9.2		8.7		
BIOCHEMISTRY					
C-reactive protein (0.0-6.0 mg/L)	340.33		201.28	27.31	11.61
Sodium (136-151 mmol/L)	122.0	128.0	139	139.0	141.0
Potassium (3.5-5.6 mmol/L)	5.9	5.7	5.3	5.0	5.0
Chloride (97-108 mmol/L)	96	105.0	111.0	111.0	110.0
Calcium (2.02-2.60 mmol/L)	2.08	2.06	2.13	1.79	1.98
Phosphorus (0.8-1.5 mmol/L)	0.81			1.9	
Magnesium (0.7-1.06 mmol/L)	0.35			0.5	
Albumin (35-52 g/L)				24.3	
Blood urea nitrogen (2.8-8.3 mmol/L)	11.3		9.4		
Creatinine (44-135 mcmol/L)	202.0		139.0	115.0	
Glucose (3.5-6.2 mmol/L)	2.4	8.0	4.6		
Fibrinogen (<4.5 g/L)	5.71		4.79	3.54	
Alkaline Phosphatase (28-220 U/L)	78				
Lactate dehydrogenase (0-250 U/L)	250			258.0	210.0
Uric Acid (155-428 mmol/L)	442.0				
Alanine transaminase (0-45 U/L)	30				
Aspartate aminotransferase (0-38 U/l)	93		124		
Ferritin (10-120 mcg/L)	700.2		670.1	697.9	647.8
COAGULATION					
International normalized ratio (<1.2)	1.08				
Partial thromboplastin time (seconds)	14.1				
Partial thromboplastin time (70-110 %)	89.0				
D-dimer (0.0-0.5 mcg/mL)	3.69		2.38	1.3	

venous methylprednisolone 60 mg TID was commenced. Intravenous infusion of lactated Ringer's solution, 0.9% normal saline, and 5% glucose solution was started. A resolution of the hyponatraemia and hyperkalaemia was noticed within 72 hours. Then the dose of the administered corticosteroid was reduced. At five days, the patient was stable and did not require oxygen therapy.

Outcome and follow-up

The patient showed improvement in her general condition, and on the tenth day of her hospitalization, which was more than 14 days from the onset of symptoms, she was considered clinically recovered and discharged with a follow-up on an outpatient basis. She was continued with dehydrocortisone 15 mg orally daily and advised to reduce the dose in one week, fludrocortisone 0.05 mg daily, oral calcium supplements, calcitriol, and magnesium sulphate as a replacement therapy for the hypocorticism and hypoparathyroidism.

DISCUSSION

In this paper, we report a demonstrative case of APS-1 that displayed several features described in the literature and presented with an adrenal crisis precipitated by SARS-CoV-2 infection.

Since late December 2019, cases of the novel COVID-19 infection have reached pandemic levels. In the early phase of the infection, appropriate immune responses terminate the viral replication and prevent the disease progression. If the infection is not eliminated, the disease enters into the severe inflammatory response phase. Cytokine storm and elevated inflammatory markers produced by innate immune cells might induce pulmonary fibrosis, dyspnea, reduction in oxygen saturation, and systemic injuries resulting in acute respiratory distress syndrome (ARDS).[11] ARDS is the main cause of death in patients with SARS-CoV-2 infection.[9]

A retrospective study reported thrombotic rates of 31% in critically ill patients[12] and heightened the need of therapeutic doses of low molecular weight heparin in COVID-19 patients with elevated D-dimer levels. Given the coagulation abnormalities associated with glucocorticoid use[13] and concerns over the disseminated thromboembolic disease in severe COVID-19[14], low molecular weight heparin was introduced to our patient.

Patients with primary adrenal insufficiency are at increased risk of infections[15] due to the defective action of neutrophils and natural killer cells[16] that compromises innate immune response. Glucocorticoids are known to have both stimulating and inhibitory effects on the immune response. In the initial phases of an infection, physiological glucocorticoid concentrations mobilize the immune system. In turn, this response activates the hypothalamic-pituitary-adrenal (HPA) axis to mild immunosuppression to reduce cytokine toxicity[17], thus preventing hyperinflammatory syndromes.

Recent studies from Finland show that patients with APS-1 have increased mortality from infections in comparison to the general population.[18] Their risk of severe COVID-19 infection is also enhanced because they have autoantibodies against type 1 interferons[19], which play a crucial role in COVID-19 protection by limiting viral growth[20].

For this reason, the European Society of Endocrinology stated that patients with adrenal insufficiency may be at higher risk of medical complications and at increased mortality risk in the case of COVID-19 infection.[21,22] The compromised immune response may contribute to the worsening of the COVID-19 infection and the development of ARDS. However, they reported that data on COVID-19 presentation and outcome in adrenal insufficient subjects are lacking. Later that year, Carosi et al. concluded in a retrospective study that patients who are effectively treated and trained appear to have the same incidence and severity of COVID-19 as controls.[23]

Our patient presented with the classic manifestations of adrenal crisis - hypotensive shock, electrolyte disturbances of hyponatremia and hyperkalemia, and hypoglycemia.

Treatment in adrenal crisis is aimed first at hemodynamic stabilization followed by a stress dose hydrocortisone. In our patient's case, she received fluid resuscitation and methylprednisolone as hydrocortisone is not available in our country. We chose methylprednisolone over dexamethasone because of its mineralcorticoid potency.[24] The initiation of the systemic steroid was crucial in the management of this patient as it corrected adrenal insufficiency and also alleviated the hyperinflammatory state of COVID-19.[25] Data from randomized trials enhance the role of glucocorticoids for severe COVID-19. In a meta-analysis of seven trials that included 1703 critically ill patients with COVID-19, glucocorticoids reduced 28-day mortality compared with the standard care or placebo and were not associated with an increased risk of severe adverse events.[26] In another systematic review and network meta-analysis of randomized trials, glucocorticoids were the only intervention for which there was at least moderate certainty of a mortality reduction compared with standard care.[27]

Unfortunately, a delayed diagnosis of Addison's disease and APS is still common. According to a cross-sectional study of 216 patients with adrenal insufficiency, less than 50% of the patients were correctly diagnosed within the first half year after symptoms appeared, and it took over 5 years until 20% of the patients were diagnosed.[28] Observing evidence of a single-component disease of APS-1 should raise high clinical suspicion for the existence of other autoimmune disorders. Screening for organ-specific autoantibodies and end-organ functional tests of patients and relatives is valuable as in some cases, prompt recognition of the disease and early treatment is vital. Because decades may pass before the appearance of all manifestations, which cannot be predicted, lifelong follow-up is strongly recommended.

CONCLUSIONS

Our case report illustrates the increased risk of severe course of COVID-19 in APS-1 syndrome patients. It is important to recognize SARS-CoV-2 as a possible cause for endocrinological failure exacerbation, as early diagnosis is crucial for adequate treatment. The case reinforced the significance of a timely diagnosis, appropriate treatment, and education of patients with such a rare condition like APS-1.

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Адреналовый криз, индуцированный SARS-CoV-2, у пациента с аутоиммунным полигландулярным синдромом 1 типа: клинический случай

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Резюме

Аутоиммунные полигландулярные синдромы (АПС) – редкие заболевания, характеризующиеся сосуществованием эндокринных и неэндокринных дисфункций, опосредованных аутоиммунными механизмами. Аутоиммунный полигландулярный синдром 1 типа определяется как сосуществование хронического кожно-слизистого кандидоза, гипопаратиреоза и аутоиммунной надпочечниковой недостаточности. Болезнь Аддисона как обязательный компонент потенциально опасна для жизни.

Здесь мы демонстрируем случай 44-летней женщины с АПС-1 (гипопаратиреоз, надпочечниковая недостаточность, гипергонадотропный гипогонадизм) и адреналовым кризом, вызванным SARS-CoV-2. У больной типичны проявления гипотензивного шока, электролитных нарушений гипонатриемии и гиперкалиемии, гипогликемии.

Наш клинический случай иллюстрирует повышенный риск тяжёлого течения COVID-19 у пациентов с синдромом АПС-1 наряду с повышенной подверженностью медицинским осложнениям. Этот случай подтвердил важность своевременной диагностики, соответствующего лечения и обучения пациентов с таким редким заболеванием, как АПС-1.

Ключевые слова

адреналовый криз, АПС-1, COVID-19