TJEM TURKISH JOURNAL OF ENDOCRINOLOGY AND METABOLISM

CASE REPORT
Turk J Endocrinol Metab. 2022;26(4):217-220

Successful Treatment of Diabetic Ketoacidosis in a Patient with Insulin Allergy and Coronavirus Disease 2019: A Case Report

ABSTRACT

Diabetic ketoacidosis is a frequent hyperglycemic emergency. During the coronavirus disease 2019 pandemic, researchers showed a higher prevalence of diabetic ketoacidosis and mortality compared with the preceding years. It is expected that lung involvement in coronavirus disease 2019 decreases compensation capacity for ketoacidosis. Thus, management of the diabetic ketoacidosis is critical in patients with coronavirus disease 2019. Insulin allergy makes the treatment procedure more complicated in these patients. Desensitization procedures or immunomodulatory therapies are not a routine part of treating diabetic ketoacidosis due to the urgency of the disease. Insulin administration to patients with insulin allergy and coronavirus disease 2019 may cause a risk of decreased maintaining oxygenation and compensating for ketoacidosis and endanger airway safety due to possible anaphylaxis. Clinicians should check all preparations for a possible need for anaphylaxis treatment and difficult airway management, including invasive procedures before insulin therapy. Here, we wanted to share a case of successful treatment of diabetic ketoacidosis in a patient with insulin allergy and coronavirus disease 2019.

Keywords: COVID-19, diabetic ketoacidosis, hypersensitivity, insulin, SARS-CoV-2

Introduction

Diabetic ketoacidosis (DKA) is the most common hyperglycemic emergency in patients with diabetes mellitus (DM).[1] The diagnosis of the DKA depends on hyperglycemia, high urinary or blood ketoacids, and a high anion gap metabolic acidosis.[2] In the era of the coronavirus disease 2019 (COVID-19) pandemic, many researchers revealed that a significant part of diabetic patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) got admitted to emergency departments due to DKA.[3,4] Furthermore, the coexistence of DKA and COVID-19 worsens the clinical outcomes of both clinical conditions.[5,6] The mainstays of treatment in patients with DKA include treatment of any underlying precipitating event, restoring circulating volume, electrolyte replacement, and insulin therapy. However, managing this emergency condition becomes complicated in patients with insulin allergies.[7] Although developments in insulin production technology have reduced the incidence of insulin allergy in recent decades, the rate of insulin allergy varies between 0.1% and 7.1%.[8-10] Insulin therapy might be safely provided in allergic patients after insulin desensitization or immunosuppressant therapies, but using these modalities is not a regular part of treating patients with DKA due to the disease's urgency.[10,11] Here, we described a critically ill patient with COVID-19 and insulin allergy in which severe DKA resolved after initiation of continuous intravenous (IV) recombinant human insulin infusion.

Case Presentation

A 67-year-old woman with hypertension, type 2 DM, and insulin allergy was admitted to the emergency department with complaints of fatigue, dyspnea, nausea, and vomiting. Her medications were losartan potassium (1×50 mg), metformin HCl (2×1000 mg), and gliclazide (1×80 mg). She was diagnosed with an allergy to insulin aspart 8 years ago by symptoms such as pruritus, skin rash, hoarseness, dyspnea, and swelling of the tongue and lips after insulin administration. A skin prick test confirmed the diagnosis and revealed the allergy to the antihistamine agents. At the first examination, the patient had tachycardia (130 bpm), tachypnea (36/min), and mild hypoxemia (SpO_2: 87%). The fingertip sampling revealed high blood glucose of 478 mg/dL (Table 1). There was no significant finding in electrocardiography

Doğukan Şenberber[1]
Mehmet Nuri Yakar[1]
Dilan Delibalta[2]
Tevfik Demir[2]
Ali Necati Gökmen[1]

[1]*Department of Anaesthesiology and Reanimation, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey*
[2]*Department of Internal Medicine, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey*

Corresponding author:
Mehmet Nuri Yakar
✉ dr.nuriyakar@gmail.com

Received: January 12, 2022
Accepted: August 16, 2022
Publication Date: December 1, 2022

Cite this article as: Şenberber D, Yakar MN, Delibalta D, Demir T, Gökmen AN. Successful treatment of diabetic ketoacidosis in a patient with insulin allergy and coronavirus disease 2019: A case report. *Turk J Endocrinol Metab.* 2022;26(4):217-220.

DOI: 10.5152/tjem.2022.22035

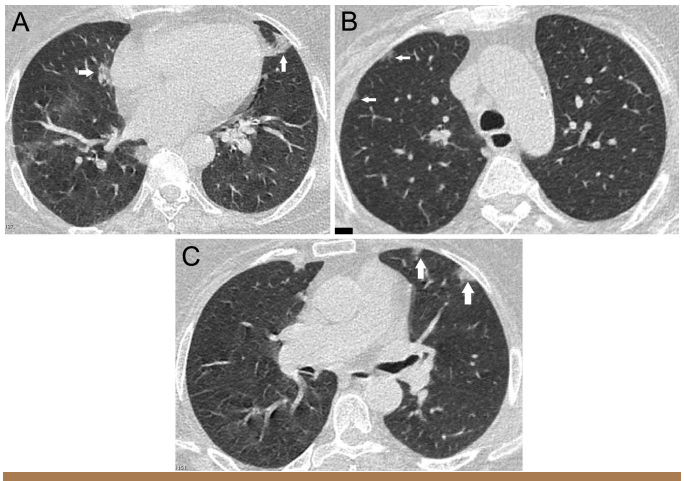

Figure 1. (A-C) The ground glass opacities (marked with white arrows) which are conscious for the coronavirus disease 2019 diagnosis located in subpleural, peripheral, and pericardiac zones.

and bedside echocardiography except tachycardia. Arterial blood gas analysis revealed a high anion gap metabolic acidosis (pH: 6.96, PCO_2: 21.6 mmHg, PaO_2: 66.8 mmHg, lactate: 2.4 mmol/L, HCO_3: 6.8 mmol/L, Na: 139 mmol/L, K: 4.9 mmol/L, SO_2: 86.2%). Also, laboratory tests showed ketonuria and a high HbA1c rate of 12.9. The patient was diagnosed with DKA, and isotonic saline infusion was started with a rate of 20 mL/kg/h for the first 2 hours. Additionally, 100 mmol sodium bicarbonate was infused over 2 h with 20 mEq potassium chloride. By the way, nasopharyngeal sampling for the real time-polymerase chain reaction (RT-PCR) test and a non-contrast-enhanced chest computed tomography (CT) were planned due to unexplained hypoxemia and COVID-19 pandemic conditions. The chest CT scan revealed multilobar, multifocal subpleural ground-glass opacities, which are suspicious for COVID-19 (Figure 1A-C), and the RT-PCR test confirmed the disease. Then, the patient was transferred to the intensive care unit (ICU).

After 2000 mL crystalloid resuscitation, heart and respiratory rates reduced to 120 bpm and 28/min, respectively. Laboratory analysis on admission showed mild regression of metabolic acidosis and blood glucose level (pH: 7.07, PCO_2: 17.3 mmHg, HCO_3: 7.8 mmol, K: 4.06 mmol/L, glucose: 413 mg/dL). Under 8 L/min oxygen therapy via nasal cannula, oxygenation was normal (PaO_2: 98 mmHg). The isotonic saline infusion was reduced to 200 mL/h, and the molar sodium bicarbonate infusion was stopped. According to recommendations in the national COVID-19 guidelines, enoxaparin, pantoprazole, and favipiravir therapies were started.

MAIN POINTS

- The coexistence of diabetic ketoacidosis and coronavirus disease 2019 worsens the clinical outcomes of both clinical conditions. Also, managing the DKA becomes complicated in patients with insulin allergy.
- The increased work of breathing due to lung involvement of SARS-CoV-2 may limit the respiratory compensation of ketoacidosis.
- Insulin administration in patients with insulin allergy may cause angioedema of the larynx, upper airway, or tongue resulting in difficult airway who cannot be intubated or ventilated.
- The treatment procedures should be applied under close monitoring and after preparation for difficult intubation or advanced airway management.

An intensivist and endocrinologist evaluated the patient multidisciplinary for planning the insulin therapy. The patient and the next of kin were informed about the insulin treatment process, complications, intubation risk, and possible surgical intervention such as cricothyroidotomy, and written informed consent was obtained. Although it might increase the blood glucose level in the first step, methylprednisolone was applied with a 1 mg/kg dose, considering the benefits of anaphylaxis prophylaxis. We avoided using antihistamines to prevent any allergic reactions. Before the insulin administration, vascular accesses, all equipment, and medications, including adrenalin with appropriate dose and concentration, were checked that might be needed to treat anaphylaxis, rapid sequence intubation, and advanced airway management. Then, regular insulin was chosen for subcutaneous administration with a dose of 0.1 IU/kg, and the patient was closely monitored for the risk of possible anaphylaxis. After 30 minutes of close monitoring, there was no sign of anaphylaxis or allergic reaction. Then, we started regular insulin infusion with a 0.1 IU/kg/h rate. Additionally, 30 mEq potassium chloride replacement was provided per liter. Insulin infusion was set according to fingertip glucose checks and did not need an insulin bolus.

On the 8th hour of ICU follow-up, we realized the swelling of the patient's lips. Insulin infusion was stopped. Reexamination of the patient did not indicate any sign of anaphylaxis. Oropharyngeal examination and tongue were normal. There was no pruritis, hoarseness, dyspnea, or hypotension. The analysis did not reveal any laboratory worsening (pH: 7.22, PCO_2: 24.3 mmHg, PaO_2: 89 mmHg, HCO_3: 12.3 mmol/L, K: 3.6 mmol/L, glucose: 221 mg/dL). We decided to apply 40 mg of additional methylprednisolone and continue potassium chloride replacement. One hour later, there was no other reaction, and swelling of lips was mildly recovered. The blood glucose level was 226 mg/dL, and we restarted the regular insulin infusion. After the blood glucose level reached under 200 mg/dL, insulin infusion was maintained with an appropriate rate that provided a blood glucose level between 150 and 200 mg/dL. After achieving the target blood glucose level, we decided to apply dexamethasone with a dose of 6 mg/day.

Diabetic ketoacidosis resolved on the second day of the ICU follow-up (pH: 7.40, PCO_2: 32.8 mmHg, PaO_2: 89.6 mmHg, HCO_3: 21.3 mmol, K: 3.9 mmol, SO_2: 99.2%). Lips swelling recovered. Oral nutrition was started. Although we planned high nutritional support to achieve the target calorie, on the third day of ICU admission, ++ ketonuria persevered. It might be related to the catabolic process secondary to the infection, as well as decreased oral intake in the periods of increased work of breathing. However, she did not need any support that required ICU stay except conventional oxygen therapy. She was discharged to the ward on the third day of ICU follow-up with no additional complications. The patient was discharged from the ward with a prescription of insulin NPH (2× 50 IU/day, subcutaneous), metformin (2×1000 mg/day, peroral), dapagliflozin propanediol monohydrate (1×10 mg/day, peroral), pioglitazone HCl (1×30 mg/day, peroral), and glucagon HCl for a possible hypoglycemic emergency.

Table 1. Laboratory Findings From Hospital Admission to ICU Discharge

	First day				Second day				Third day			
pH	6.96		7.22		7.30		7.40		7.41		7.37	
$PaCO_2$, mmHg	21.6		24.3		29.3		32.8		35.0		36.0	
PaO_2, mmHg	66.8		89.0		82.8		89.6		78.6		81.1	
HCO_3, mmol/L	6.8		12.3		16.8		21.3		25.8		24.2	
Lactate, mmol/L	2.4		N/A		N/A		N/A		0.7		0.9	
SO_2, %	86.2		96.0		96.2		99.2		98.1		98.0	
Serum sodium, mEq/L	139		149		153		148		146		138	
Serum potassium, mEq/L	4.9		4.1		3.7		3.4		3.9		3.6	
Serum chloride, mEq/L	103		110		119		114		111		107	
Serum phosphorus, mg/dL	4.39				N/A				2.86			
Anion gap, mEq/L	34.1		30.8		20.9		16.1		13.1		10.4	
Glucose, mg/dL	478	413	364	221	219	241	226	202	180	189	165	172
Urine ketone	+++	+++	+++	+++	+++	+++	++	++	++	++	++	++
BUN, mg/dL	22.5				20.4				12.5			
sCr, mg/dL	0.95				0.77				0.62			
WBC × 10^3/μL	9.8				12.2				9.9			
Hemoglobin, g/dL	14.2				11.6				11.1			
Hematocrit, %	46.0				36.1				33.7			
Platelet × 10^3/μL	295.0				267.0				230.0			
Ferritin, ng/mL	69.8				87.3				84.3			
D-dimer, μg/mL	1.23				1.71				1.25			
CRP, mg/L	7.5				11.8				13.7			
Procalcitonin, ng/mL	0.06				0.43				0.30			

BUN, blood urea nitrogen; CRP, C-reactive protein; ICU, intensive care unit; PaCO2, partial pressure of arterial carbon dioxide; N/A, not applicable; PaO2, partial pressure of arterial oxygen; SO2, arterial oxygen saturation; sCr, serum creatinine; WBC, white blood cell.

All procedures performed in this case report followed the Helsinki Declaration's ethical standards. Written informed consent was obtained from the patient to publish this case report.

Discussion

In this case report, we aimed to share our experiences of DKA management in a critically ill patient with COVID-19 and insulin allergy. Diabetes mellitus is a risk factor for poor clinical course and mortality in patients with COVID-19,[12] and SARS-CoV-2 infection is associated with a higher risk of presenting with DKA, especially in people with pre-existing type 2 diabetes and newly diagnosed diabetes.[4,13] Also, the coexistence of DKA and SARS-CoV-2 infection is related to having a longer time to resolution of DKA with higher mortality.[3-6] All these consequences emphasize the importance of early diagnosis and administration of the therapies aiming to resolve DKA early and reduce mortality while treating COVID-19.

Insulin allergy rarely occurs. In the last decades, development in insulin production methods, especially the widespread use of recombinant insulin, decreased the rate of adverse reactions.[8-10] The symptoms in a patient with insulin allergy range from local injection site reactions (urticaria, pruritis, erythema, swelling at the injection site, etc.) to severe generalized anaphylactic reactions.[10] Co-existing insulin allergy in a patient with DKA can make the treatment procedures more complicated. In non-urgent cases, changing insulin preparation, insulin desensitization, and immunosuppressant therapies are the alternatives.[8,10,11] The desensitization procedure is based on administering initial essential insulin doses intravenously or subcutaneously that gradually be increased by hours.[14,15] In our case, we applied 0.1 IU/kg regular insulin subcutaneously with close monitoring and preparations to treat possible anaphylaxis and procedures such as advanced airway management. Before insulin administration, we also applied methylprednisolone in a 1 mg/kg dose by considering the harm and benefit. Corticosteroids induce hyperglycemia in diabetic patients and may worsen the condition of DKA.[1] Premedication is not routinely recommended before desensitization procedures, but we applied methylprednisolone due to the relatively high initial subcutaneous insulin dose compared with a usual desensitization procedure and the patient's allergy to the antihistamines. Additionally, immunosuppressant therapies were not reasonable alternatives due to active SARS-CoV-2 infection. However, corticosteroids, especially dexamethasone, reduce mortality and the need for mechanical ventilation in patients with COVID-19.[16]

The increased work of breathing due to lung involvement of SARS-CoV-2 may limit the respiratory compensation of ketoacidosis. Despite severe acidosis and increased work of breathing, conventional oxygen therapy was enough for normoxia owing to a mild COVID-19 involvement of the lungs in our patient. However, the patient had a limited compensation capacity against respiratory failure caused by possible anaphylaxis or less severe reactions that would be seen after the initiation of insulin therapy. Additionally, a patient with angioedema of the larynx, upper airway, or tongue that results in airway obstruction is a candidate for a difficult airway who cannot be intubated or ventilated.[17] For these reasons, we prepared the medications, equipment, and the patient, for possible difficult intubation and advanced airway maneuvers such as cricothyroidotomy.

The present case report has some limitations, including a rare combination of COVID-19, insulin allergy, and DKA. The treatment modalities in this article cannot be generalized. An individualized treatment process should be planned for each patient. In this case, the diagnosis of insulin allergy depends on a prick test performed 8 years ago. The patient did not have a recent prick test. Due to our center's laboratory policy and the patient's urgency, we could not confirm the diagnosis with additional tests such as specific Ig E in night shift. Additionally, the prescription of insulin NPH on discharge and no need for methylprednisolone may indicate a suspicion about the insulin allergy diagnosis. Tongue and lip swelling after insulin administration supports an allergic reaction, even if it is caused due to additive agents. Beyond that, the case report has strengths because this article highlights how to manage increased work of breathing in a COVID-19 patient with DKA who had no option except insulin administration despite an insulin allergy history in the limited circumstances for insulin allergy diagnosis confirmation.

In conclusion, COVID-19 should also be excluded in patients admitted to the hospital due to DKA in the era of the COVID-19 pandemic. The treatment of DKA in patients with insulin allergy is complicated in addition to the limited compensation capacity of ketoacidosis due to lung involvement of COVID-19. Also, treatment procedures should be applied under close monitoring and after preparation for difficult intubation or advanced airway management.

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.N.Y., D.Ş.; Design – D.Ş., M.N.Y., D.D.; Supervision – M.N.Y., T.D., A.N.G.; Resources – D.Ş., DD.; Materials – D.Ş.; Data Collection and/or Processing – D.Ş., D.D., M.N.Y.; Analysis and/or Interpretation – M.N.Y.; Literature Search – D.Ş., D.D., M.N.Y.; Writing Manuscript – D.Ş., D.D., M.N.Y.; Critical Review – M.N.Y., T.D., A.N.G.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This study received no funding.

The authors declare that the paper's abstract has been sent as an oral presentation at Internal Medicine Winter School planned to be held in Antalya, Belek, on February 10-13, 2022.

References

1. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. *Nat Rev Dis Primers*. 2020;6(1):40. [CrossRef]
2. Schwarzfuchs D, Rabaev E, Sagy I, et al. Clinical and epidemiological characteristics of diabetic ketoacidosis in older adults. *J Am Geriatr Soc*. 2020;68(6):1256-1261. [CrossRef]
3. Pasquel FJ, Messler J, Booth R, et al. Characteristics of and mortality associated with diabetic ketoacidosis among US patients hospitalized with or without COVID-19. *JAMA Netw Open*. 2021;4(3):e211091. [CrossRef]
4. Croft A, Bucca A, Jansen JH, et al. First-time diabetic ketoacidosis in Type 2 diabetics with Covid-19 infection: a novel case series. *J Emerg Med*. 2020;59(5):e193-e197. [CrossRef]
5. Chamorro-Pareja N, Parthasarathy S, Annam J, Hoffman J, Coyle C, Kishore P. Letter to the editor: unexpected high mortality in COVID-19 and diabetic ketoacidosis. *Metabolism*. 2020;110:154301. [CrossRef]
6. 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]
7. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19(suppl 27):155-177. [CrossRef]
8. Radermecker RP, Scheen AJ. Allergy reactions to insulin: effects of continuous subcutaneous insulin infusion and insulin analogues. *Diabetes Metab Res Rev*. 2007;23(5):348-355. [CrossRef]
9. Ghazavi MK, Johnston GA. Insulin allergy. *Clin Dermatol*. 2011;29(3):300-305. [CrossRef]
10. Heinzerling L, Raile K, Rochlitz H, Zuberbier T, Worm M. Insulin allergy: clinical manifestations and management strategies. *Allergy*. 2008;63(2):148-155. [CrossRef]
11. Yong PFK, Malik R, Arif S, et al. Rituximab and omalizumab in severe, refractory insulin allergy. *N Engl J Med*. 2009;360(10):1045-1047. [CrossRef]
12. Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr*. 2020;14(4):535-545. [CrossRef]
13. Misra S, Barron E, Vamos E, et al. Temporal trends in emergency admissions for diabetic ketoacidosis in people with diabetes in England before and during the COVID-19 pandemic: a population-based study. *Lancet Diabetes Endocrinol*. 2021;9(10):671-680. [CrossRef]
14. Asai M, Yoshida M, Miura Y. Immunologic tolerance to intravenously injected insulin. *N Engl J Med*. 2006;354(3):307-309. [CrossRef]
15. Nguyen AD, Luong CQ, Chu HC, et al. Successful management of severe diabetic ketoacidosis in a patient with type 2 diabetes with insulin allergy: a case report. *BMC Endocr Disord*. 2019;19(1):121. [CrossRef]
16. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. [CrossRef]
17. Simons FER, Ardusso LRF, Bilò MB, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol*. 2011;127(3):587-93.e1. [CrossRef]