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CASE REPORT

Clinical features resembling subcutaneous insulin resistance observed in a patient with type 2 diabetes and severe COVID-19-associated pneumonia: a case report

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Abstract

We report the case of a 52-year-old hyperglycemic woman with type 2 diabetes and severe coronavirus disease 2019 (COVID-19)-associated pneumonia, possibly involving the subcutaneous insulin resistance (SIR) syndrome. After admission for pneumonia, her average daily blood glucose (BG) levels remained at 300–400 mg/dL, although the required dosage of subcutaneous insulin markedly increased (~ 150 units/day; ~ 2.63 units/kg/day). Furthermore, the patient had generalized edema along with hypoalbuminemia, developed extensive abdominal purpuras, and had increased plasma D-dimer levels during treatment, suggestive of coagulation abnormalities. Therefore, intravenous infusion of regular insulin was initiated. The BG level subsequently decreased to < 200 mg/dL 2 days after administering 18 units/day of insulin infusion and 118 units/day of subcutaneous insulin, suggesting that subcutaneous insulin alone might have been ineffective in reducing hyperglycemia, which is clinically consistent with the characteristics of an SIR syndrome. Impaired skin microcirculation arising from coagulation abnormalities, subcutaneous edema associated with inflammation-related hypoalbuminemia or vascular hyperpermeability, and/or reduction in subcutaneous blood flow due to COVID-19-induced downregulation of angiotensin-converting enzyme 2 might be associated with the development of pathological conditions that resemble SIR syndrome, leading to impaired subcutaneous insulin absorption.

Keywords Coronavirus disease 2019 (COVID-19)-associated pneumonia · Subcutaneous blood flow · Subcutaneous insulin resistance · Type 2 diabetes

Introduction

Diabetes mellitus is associated with increased severity and mortality in patients with coronavirus disease 2019 (COVID-19)-associated pneumonia. In contrast to critical illness induced by other conditions, people with type 2 diabetes experiencing severe COVID-19-associated pneumonia reportedly require much larger amounts of insulin [1]. A recent study demonstrated that insulin infusion may be an effective method for achieving glycemic targets in hyperglycemic patients with COVID-19-associated pneumonia [2]. We recently encountered a severe COVID-19-associated

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pneumonia patient with hyperglycemia refractory to copious insulin injections. Treatment with intravenous insulin infusion caused rapid improvement in hyperglycemia, suggesting the involvement of the subcutaneous insulin resistance (SIR) syndrome.

Case report

A 52-year-old woman diagnosed with type 2 diabetes 10 years ago and recently treated with vildagliptin (100 mg/day), repaglinide (1.5 mg/day), and metformin (1500 mg/day) was admitted to our hospital with complaints of fever, cough, and dyspnea over the preceding 5 days. On admission, COVID-19-associated pneumonia was diagnosed based on chest X-ray and chest computed tomography images (Supplementary Figs. 1 and 2) as well as reverse transcription polymerase chain reaction testing. The patient's height, weight, and body mass index were 165 cm, 57 kg, and 20.9 kg/m^2, respectively. Initial laboratory examination results were negative for urine ketones, with casual plasma glucose, glycated hemoglobin A1c, and serum creatinine levels of 268 mg/dL, 8.3% (67 mmol/mol), and 0.57 mg/dL, respectively (Table 1). The fasting serum C-peptide level was 1.92 ng/mL (plasma glucose, 205 mg/dL) after recovery from the COVID-19-associated pneumonia (on the 32nd hospital day). No diabetic complications were observed. Although the antiviral agent (favipiravir) and inhaled corticosteroid (ciclesonide) were administered after admission, radiological findings worsened, indicating severe COVID-19-associated pneumonia (Supplementary Fig. 1b). Consequently, mechanical ventilation and extracorporeal membrane oxygenation (ECMO) with heparin were initiated on the 4th and 11th days, respectively. Pulse methylprednisolone therapy (1000 mg/day) was delivered intravenously from the 13th to the 15th day, followed by intravenous prednisolone (60 mg/day). On the 18th day, the patient's respiratory condition improved, and ECMO was discontinued. Intravenous prednisolone was gradually tapered and stopped on the 32nd day.

The time courses of serum albumin levels and the daily doses of subcutaneous insulin from admission until the initiation of intravenous insulin infusion were mirror images of each other; the albumin level decreased to 1.4 g/dL and generalized edema occurred during the course of ECMO (Supplementary Fig. 3c).

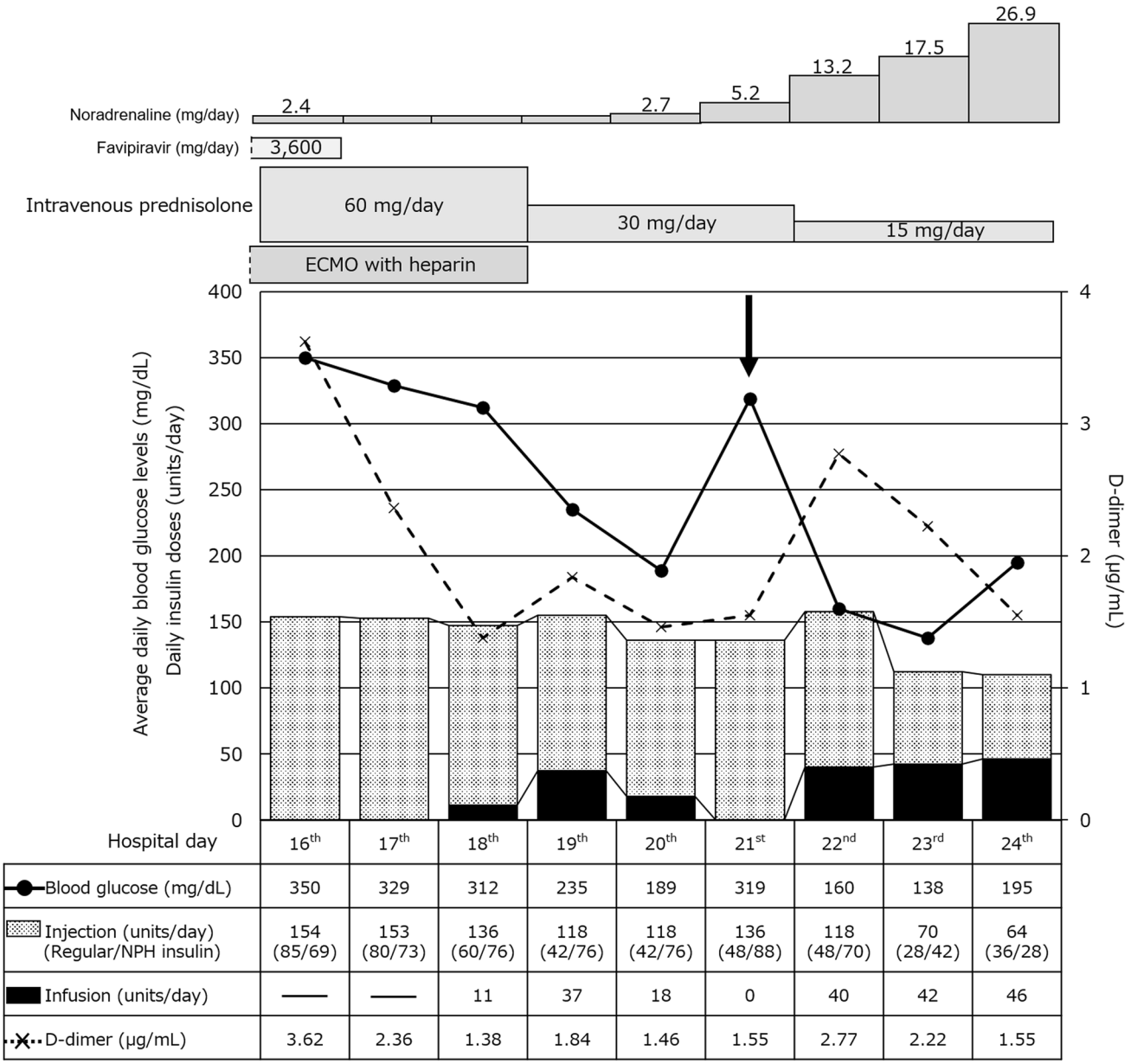
Glycemic control involves discontinuing oral hypoglycemic agents on admission and initiating multiple daily subcutaneous injections of regular and neutral protamine Hagedorn (NPH) insulin. Although the necessity for subcutaneous insulin had increased to extremely high doses by the 17th day (~150 units/day; ~2.63 units/kg/day), average daily blood glucose (BG) levels remained at 300–400 mg/dL, while the patient received 900 kcal/day enteral nutrition (Fig. 1 and Supplementary Fig. 3d). It appeared that the increased insulin requirement was not solely due to insulin resistance induced by pulse methylprednisolone (1000 mg/day) and intravenous prednisolone (60 mg/day). Intriguingly,

Table 1 Laboratory data on admission

Urine			Biochemistry			Diabetes-related		
PRO	(−)		ALB	4.0	g/dL	Plasma glucose	268	mg/dL
GLU	(±)		T-Bil	0.6	mg/dL	HbA1c	8.3	%
KET	(−)		AST	132	U/L	Anti-GAD Ab	< 5.0	U/mL
BLD	(−)		ALT	169	U/L			
			γGTP	84	U/L	Blood gas analysis[a] (room air)		
CBC			LDH	364	U/L	pH	7.555	
WBC	5,900	/μL	ALP	176	U/L	pO_2	34.1	mmHg
RBC	553	$\times 10^4$ /μL	AMY	79	U/L	pCO_2	58	mmHg
Hb	16.9	g/dL	CK	41	U/L	HCO_3^-	30.2	mmol/L
Hct	48.3	%	BUN	13.2	mg/dL			
Plt	7.7	$\times 10^4$ /μL	Cr	0.57	mg/dL	PCR test (nasal swab)		
			eGFR	85.3	mL/min/1.73m^2	SARS-Cov-2	Positive	
Coagulation			Na	136	mEq/L			
APTT	42.7	seconds	K	4.2	mEq/L			
PT	11.9	seconds	Cl	95	mEq/L			
PT-INR	0.98		CRP	5.33	mg/dL			
D-dimer	0.96	μg/mL						

Anti-GAD Ab anti-glutamic acid decarboxylase antibody, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

[a]The analysis was performed on the 4th hospital day



Hospital day	16th	17th	18th	19th	20th	21st	22nd	23rd	24th
Blood glucose (mg/dL)	350	329	312	235	189	319	160	138	195
Injection (units/day) (Regular/NPH insulin)	154 (85/69)	153 (80/73)	136 (60/76)	118 (42/76)	118 (42/76)	136 (48/88)	118 (48/70)	70 (28/42)	64 (36/28)
Infusion (units/day)	—	—	11	37	18	0	40	42	46
D-dimer (μg/mL)	3.62	2.36	1.38	1.84	1.46	1.55	2.77	2.22	1.55

Fig. 1 A segment of the treatment time course (16th–24th hospital days) illustrating blood glucose levels, plasma D-dimer levels, and doses of intravenously infused and subcutaneously injected insulins. The figure shows an essential segment of the treatment time course illustrating clinical parameters that strongly suggest the involvement of the SIR syndrome. By the 20th day of hospitalization, the patient's hyperglycemia improved owing to intravenous insulin infusions of 18 units/day and subcutaneous insulin injections of 118 units/day (total 136 units/day). On the 21st day, the discontinuation of intravenous insulin infusion resulted in a rapid return to the hyperglycemic state, although the total daily insulin dose was unaltered from the previous day (136 units/day) (arrow). On the following day, insulin infusions were resumed, resulting in a dramatic improvement in blood glucose levels and suggesting the existence of an SIR syndrome-like pathological condition. The solid line represents the daily average blood glucose levels calculated from the test values obtained every 2 h. The dotted line represents plasma D-dimer levels (normal range, < 1.0 μg/mL). The solid black and dotted bar graphs represent the daily doses of intravenously infused insulin and subcutaneously injected insulin, respectively. *ECMO* extracorporeal membrane oxygenation

we observed several extensive and excessive purpuras on the abdominal skin surface, with skin bulging centered at injection sites, although photographs of the skin findings could not be taken due to a lack of informed consent from the intubated patient. Accordingly, intravenous infusion of regular insulin was initiated on the 18th day. On the 20th day, the average BG level decreased to < 200 mg/dL in response to 18 units/day insulin infusion and 118 units/day subcutaneous insulin (total of 136 units/day) under 30-mg/day prednisolone treatment. Thus, on the 21st day, insulin infusion was

discontinued throughout the day. Subsequently, the average BG level rapidly increased to 319 mg/dL, although the total daily insulin dose was unchanged from the previous day (136 units/day) (Fig. 1, arrow, and Supplementary Fig. 3d, arrow). Therefore, on the following day (the 22nd day), we resumed infusion of 40 units/day insulin and continued administration of 118 units/day subcutaneous insulin. Subsequently, the average BG level rapidly decreased to 160 mg/dL with 15-mg/day prednisolone treatment. In the next 2 days, the average BG level remained stable at < 200 mg/dL with continuing insulin infusion of ≥ 40 units/day, although the dose of subcutaneous insulin was decreased to 64 units/day (Fig. 1, Supplementary Fig. 3d). These findings suggest that subcutaneous insulin alone could have been ineffective in reducing hyperglycemia, consistent with the SIR syndrome characterized by severe resistance to subcutaneous insulin but retained sensitivity to intravenous insulin [3]. Therefore, additional intravenous insulin infusion rapidly improved hyperglycemia, possibly contributing to the resolution of severe COVID-19-associated pneumonia. Thus, if an intravenous insulin infusion had been started early in the disease course, the patient might have followed a milder clinical course.

Meanwhile, we cannot deny the possibility that the improvement in glycemic control using intravenous insulin infusion could be associated with a reduction in the dose of prednisolone. However, considering that relatively higher doses (≥ 40 units/day) of intravenous insulin were consecutively required to maintain the average BG levels of < 200 mg/dL despite the fact that the prednisolone doses were reduced to 15 mg/day (on the 22nd–24th days) and 10 mg/day (on the 25th–27th days) in a phased manner, the decrease in prednisolone dose might not greatly contribute to the improvement in glycemic control (Fig. 1, Supplementary Fig. 3d).

Thereafter, we decreased the doses of intravenous insulin infusion from 46 units/day on the 27th day to 13 units/day and 16 units/day on the 28th and 29th days, respectively, as the patient showed relatively good BG levels (i.e., < 200 mg/dL); however, the average daily BG levels increased to nearly 300 mg/dL on the 29th day, suggesting the possible persistence of the SIR syndrome-like pathological conditions (Supplementary Fig. 3d, arrow head). Thus, the dose of intravenous insulin infusion was increased to 40 units/day on the 30th day along with a decrease in prednisolone dose from 10 mg/day to 5 mg/day on the 29th day, and the average daily BG levels improved to < 200 mg/dL in the next 2 days. However, as described above, the improvement in glycemic control was possibly associated with the reduction in the prednisolone dose.

Regarding other factors contributing to the sudden increase in the average BG levels on the 21st and 29th days, the type of intravenous fluids used remained the same on the indicated days. In addition, any inflammation was unlikely to increase insulin resistance as the serum C-reactive protein levels were stable on the indicated days.

Thereafter, sitagliptin and repaglinide were initiated on the 34th and 35th days, respectively, and the intravenous insulin injection was gradually decreased until it was discontinued on the 42nd day. On the 41st day, insulin degludec (10 units/day) was initiated, and the patient's BG levels eventually improved with insulin degludec (10 units/day), sitagliptin (50 mg/day), and repaglinide (1.5 mg/day).

Discussion

Most patients with SIR syndrome are young women with type 1 (insulin-dependent) diabetes [3]. In addition, SIR syndrome is characterized by diabetic ketoacidosis or persistent ketonuria, despite the administration of subcutaneous insulin, and this condition can be improved with intravenous insulin [3]. These findings are more common in patients with insulin-dependent diabetes than in those with non-insulin-dependent diabetes; owing to absolute insulin deficiency, SIR syndrome was more predominant in patients with type 1 diabetes. Therefore, SIR syndrome may be latent in some insulin-injected patients with type 2 diabetes and severe insulin resistance, similar to our patient.

This condition is thought to be primarily due to the rapid insulin degradation in the subcutaneous tissue by insulin-specific proteases [4, 5]. Paulsen et al. defined SIR syndrome according to the following three criteria: (1) resistance to the hypoglycemic action of subcutaneous insulin but not to intravenous insulin; (2) lack of increase in plasma-free insulin levels after the administration of subcutaneous insulin; and (3) increase in insulin degrading activity in the subcutaneous tissue [5]. Although our patient met the first criterion, we could not confirm whether the patient met the remaining two criteria or not, which is a limitation of this report. Thus, our patient was not definitively diagnosed with SIR syndrome, and direct evidence of the disease should be revealed in the future. However, most reported cases of SIR syndrome were clinically diagnosed, and plasma-free insulin levels after administering a subcutaneous insulin injection and insulin degradation at the tissue levels could not be determined in the cases [3]. Moreover, many studies have failed to replicate the insulin degradation activity; thus far, some studies believe it to be due to inadequate absorption and sequestration rather than insulin degradation [4, 6]. Therefore, the initially proposed pathophysiology may not necessarily be common in all cases of SIR syndrome.

In severe acute respiratory syndrome coronavirus 2-induced acute respiratory distress syndrome (ARDS), the overproduction of proinflammatory cytokines results in a cytokine storm, leading to the development of vascular

hyperpermeability [7]. Moreover, severe infection or inflammation can induce hypoalbuminemia via a decrease in albumin synthesis or increased capillary leakage associated with vascular permeability [8]. As shown in Supplementary Figs. 3c and d, the time courses of serum albumin levels and daily doses of subcutaneous insulin from admission until the initiation of intravenous insulin infusion (the 17th day) were mirror images of each other, suggesting that subcutaneous (interstitial) edema induced by hypoalbuminemia and/or vascular hyperpermeability associated with severe inflammation and/or a cytokine storm may also impair the absorption of insulin at the injection sites.

A previous study showed that critically ill patients with ARDS owing to an influenza virus developed hyperglycemia and insulin resistance during ECMO owing to the increased oxidative stress occurring throughout the extracorporeal circulation [9]. Thus, the gradual increase in subcutaneous insulin dose observed between the 11th and 18th days might be attributed to the use of ECMO in our patient. However, the direct relationship between SIR syndrome-like findings and the use of ECMO could not be assessed because an intravenous insulin was not administered during ECMO. Another likely explanation is that heparin administered during the course of ECMO might contribute to the development of the abdominal purpura, possibly leading to impaired subcutaneous insulin absorption, a phenomenon that warrants further investigation. In addition, ECMO reportedly causes a significant reduction in serum albumin levels in patients with ARDS owing to infection with an influenza virus [9]. Thus, subcutaneous (interstitial) edema induced by hypoalbuminemia associated with not only severe inflammation but also ECMO treatment might impair the absorption of insulin at injection sites.

Regarding other possible physiopathologies of SIR syndrome, a reduction in subcutaneous blood flow (SBF) is also considered to be a factor contributing to the impairment in insulin absorption at injection sites [10]. Recent studies have identified angiotensin-converting enzyme 2 (ACE2), which is expressed in the skin vasculature [11], as a receptor for severe acute respiratory syndrome coronavirus 2. Binding to the receptor results in ACE2 downregulation, leading to increased circulating angiotensin II (AT2) levels [12]. Because AT2-mediated activation of angiotensin 1 receptors may be associated with SBF reduction [13], COVID-19-induced increases in local AT2 levels may provoke SBF reduction via cutaneous vasoconstriction, thereby affecting subcutaneous insulin absorption. Concomitantly, patients with severe COVID-19-associated pneumonia reportedly present with coagulation abnormalities [7, 14]. Given that our patient developed excessive abdominal purpura and increased plasma D-dimer and fibrinogen levels during treatment (Fig. 1 and Supplementary Figs. 3a and b), coagulation abnormalities might have affected the skin microcirculation, leading to impaired subcutaneous insulin absorption, a phenomenon that warrants further investigation.

Intravenous insulin infusions are recommended for glycemic management of patients with critical illnesses [15, 16]. In our case, at the discretion of the primary infectious control doctor, enteral nutrition was administered daily via tube feeding in three divided feedings. Thus, we initially believed that subcutaneous regular insulin combined with NPH insulin might help control postprandial hyperglycemia more effectively than intravenous insulin infusions. As a result, prolonged hyperglycemia induced by avoiding the use of intravenous insulin infusions might contribute to the development of severe insulin resistance. However, if this is true, severe subcutaneous insulin resistance and severe intravenous insulin resistance must have simultaneously developed in our patient. Thus, the prolonged hyperglycemia associated with the avoidance the use of intravenous insulin infusion cannot explain the SIR syndrome-like findings.

In conclusion, in patients with type 2 diabetes and severe COVID-19-associated pneumonia, the SIR syndrome-like condition may be associated with hyperglycemia refractory to subcutaneous insulin injections. When such conditions are suspected, intravenous insulin infusion therapy may help to correct hyperglycemia.

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Author contributions AS wrote the manuscript. The other authors reviewed the manuscript and contributed to the discussion. YO is the guarantor of this work, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of data analysis. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest Akira Shimada received lecture fees from Astellas Pharm Inc., Tokyo, Japan, and Sanofi K.K., Tokyo, Japan. We report no other potential conflicts of interest relevant to this article.

Human and animal rights All procedures conducted herein were in accordance with the ethical standards of the institutional and national committees on human experimentation, as well as with the 1964 Helsinki Declaration and later versions.

Informed consent Written informed consent was obtained from the patient.

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