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CASE REPORT

A case of fulminant type 1 diabetes and protein C deficiency complicated by deep vein thrombosis

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ABSTRACT

A 25-year-old man was diagnosed with diabetic ketoacidosis (DKA) at the onset of fulminant type 1 diabetes. After acute-phase DKA treatment including placement of a central venous catheter, a massive deep vein thrombosis (DVT) and pulmonary embolism (PE) were detected on hospital day 15. His protein C (PC) activity and antigen levels were low even 33 days after completing the DKA treatment, indicating partial type I PC deficiency. Severe PC dysfunction, due to overlapping of partial PC deficiency and hyperglycemia-induced PC suppression, concomitant with dehydration and catheter treatment, may have induced the massive DVT with PE. This case suggests that anti-coagulation therapy should be combined with acute-phase DKA treatment in patients with PC deficiency, even those who have been asymptomatic. As patients with partial PC deficiency should perhaps be included among those with severe DVT complications of DKA, venous thrombosis should always be considered as a potential complication of DKA.

INTRODUCTION

Fulminant type 1 diabetes (FT1D) is characterized by an extremely rapid and almost complete destruction of β-cells, and its diagnostic criteria include diabetic ketoacidosis (DKA)[1]. Deep vein thrombosis (DVT), especially the resultant pulmonary embolism (PE), is rarely described, but can be a life-threatening complication of DKA[2,3]. DKA leads not only to dehydration and hyperglycemia, but also to coagulation abnormalities. Among them, the protein and the activity levels of protein C (PC), also known as factor XIV, reportedly decrease under hyperglycemic conditions[4,5]. PC is a vitamin K-dependent anticoagulant enzyme, the activated form of which inactivates factors V and VIII.

PC deficiency is a heritable or acquired risk factor for thrombophilia, with presentations varying from asymptomatic to venous thromboembolism, and even neonatal purpura fulminans. This disease is classified into two types: type I, a quantitative abnormality in which PC activity and antigen levels are decreased, and type II, a qualitative abnormality in which PC activity is decreased but antigen levels are maintained[6]. We report a case with DKA at the onset of FT1D, who developed massive DVT with PE after the acute-phase DKA treatment. He was subsequently diagnosed as having type I PC deficiency.

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CASE REPORT

A 25-year-old man presented to a hospital with a 2 day history of epigastric pain, nausea, and headache. His serum amylase was elevated (369 U/L), and computed tomography (CT) showed diffuse parenchymal enlargement and an indistinct pancreatic margin. He was diagnosed as having acute pancreatitis and hospitalized. He received intravenous therapy containing gabexate mesylate. On admission, the serum glucose was normal (116 mg/dL), but 3 days later, had risen to a high level (over 600 mg/dL). He was suspected to have DKA and was transferred to our hospital.

Arterial blood gas analysis showed pH 6.985 and HCO_3^- 7.4 mEq/L. His serum glucose was 1,004 mg/dL with relatively low HbA1c (6.1%). He had an extremely low serum C-peptide level (0.09 ng/mL) and 3+ urinary ketones, indicating DKA. A hemodialysis catheter was placed in his right femoral vein for 2 days to provide renal replacement therapy, because of a high potassium level (7.6 mmol/L) and dehydration. An anti-coagulant, nafamostat mesylate, was intravenously administered during renal replacement therapy. His urinary C-peptide

excretion was 1.4 μg/day, fasting and 6-min post-glucagon-stimulated serum C-peptide levels were 0.08 ng/mL and 0.11 ng/mL, respectively (Table 1). These data met the diagnostic criteria for FT1D. After continuous and intravenous insulin infusion, the therapy was switched to multiple daily insulin injections (MDII), ultimately achieving good control of blood glucose levels.

On hospital day 15, in the course of examinations to identify the cause of pancreatitis, a DVT and PE were detected coincidentally with no physical symptoms or vital sign abnormalities. The CT revealed a DVT extending from the right external iliac vein to the inferior vena cava (Figure 1). Blood tests showed elevated D-dimer (2.5 μg/mL) and fibrin/fibrinogen degradation products (FDP; 5.9 μg/mL), and decreased PC activity (46%). Neither the patient nor any of his family members had had histories of thrombotic disorders, and the results of autoantibodies were negative (Table 2). We started anticoagulation therapy; heparin (5,000 units) was administered intravenously, followed by 30 mg of an oral direct factor Xa inhibitor, rivaroxaban. The CT images showed a tendency for amelioration of the DVT and PE. D-dimer and FDP were also normalized. In contrast, PC activity (49%) and antigen (41%) levels were still low at day 33. These data allowed us to diagnose partial type I PC deficiency in this patient[6].

DISCUSSION

This case exhibited DKA at the onset of FT1D preceded by acute pancreatitis. Although he had had neither past nor family histories of thrombotic disorders, DVT and PE developed after acute-phase DKA treatment including central venous catheter placement for renal replacement therapy. His thrombosis extended from the right external iliac vein to the inferior vena cava, suggesting femoral vein catheterization to have triggered the DVT[2].

The PC activity and its antigen are reportedly reduced in patients with insulin-dependent diabetes compared with healthy controls[4]. In patients with type 2 diabetes as well, HbA1c levels are negatively associated with the plasma PC activity and antigen levels[7]. Notably, induction of hyperglycemia decreases both PC activity and antigen levels[4]. Accordingly, PC activity is reduced prior to and within 24 h in conditions of DKA, but soon normalizes after its treatment[5]. However, our case exhibited low PC activity and antigen levels even 33 days after receiving DKA treatment, when the blood glucose was well controlled with MDII therapy. At that time, he took an anticoagulant, rivaroxaban, which had no effect on his chromogenic PC assay[6]. Based on the diagnostic criteria, these laboratory data, including decreased PC activity/antigen during stable conditions, are sufficient to diagnose partial type I PC deficiency, even without genetic testing[6]. Furthermore, during acute-phase DKA, the PC activity reportedly decreases by 20–35%[4,5]. Thus,

Table 1 | Laboratory results

		Unit
Blood chemistry		
Glucose	1,004	mg/dL
HbA1c	6.1	%
Glycoalbumin	23.5	%
Amylase	136	U/L
Lipase	190	U/L
T-Bil	0.5	mg/dL
γGTP	21	U/L
AST	17	U/L
ALT	14	U/L
LDH	175	U/L
BUN	53	mg/dL
Cre	2.04	mg/dL
UA	12.6	mg/dL
TP	7	g/dL
Alb	4.5	g/dL
Na	129	mmol/L
K	7.6	mmol/L
Cl	88	mmol/L
Ca	8.9	mg/dL
CRP	1.9	mg/dL
WBC	17,100	/μL
Hb	14.6	g/dL
Plt	230×10^3	/μL
Urinalysis		
Ketone body	3+	
Protein	±	
Glucose	4+	
Arterial blood gas analysis		
Ph	6.985	
PCO_2	32.7	mmHg
HCO_3^-	7.4	mmol/L
Base excess	−24.4	mmol/L
Insulin secretory ability		
Serum CPR	0.09	ng/mL
Urinary CPR (day 8)	1.4	μg/day
Glucagon loading test (day 12)		
CPR 0 min	0.08	ng/mL
CPR 6 min	0.11	ng/mL
Islet-related autoantibody		
Anti-GAD antibody	13.2 (day 1) 5.6 (day 29)	U/mL
Anti-IA-2 antibody	<0.4	U/mL
Anti-Insulin antibody	<0.4	%
Anti-ZnT8 antibody	<15.0	U/mL
HLA typing		
HLA-DRB1	*15:02/*13:02	
HLA-DQB1	*06:01:01/*06:04:01	

CPR, C-peptide immunoreactivity; GAD, glutamic acid decarboxylase; HLA, human leukocyte antigen; IA-2, insulinoma-associated antigen-2; ZnT8, zinc transporter 8.

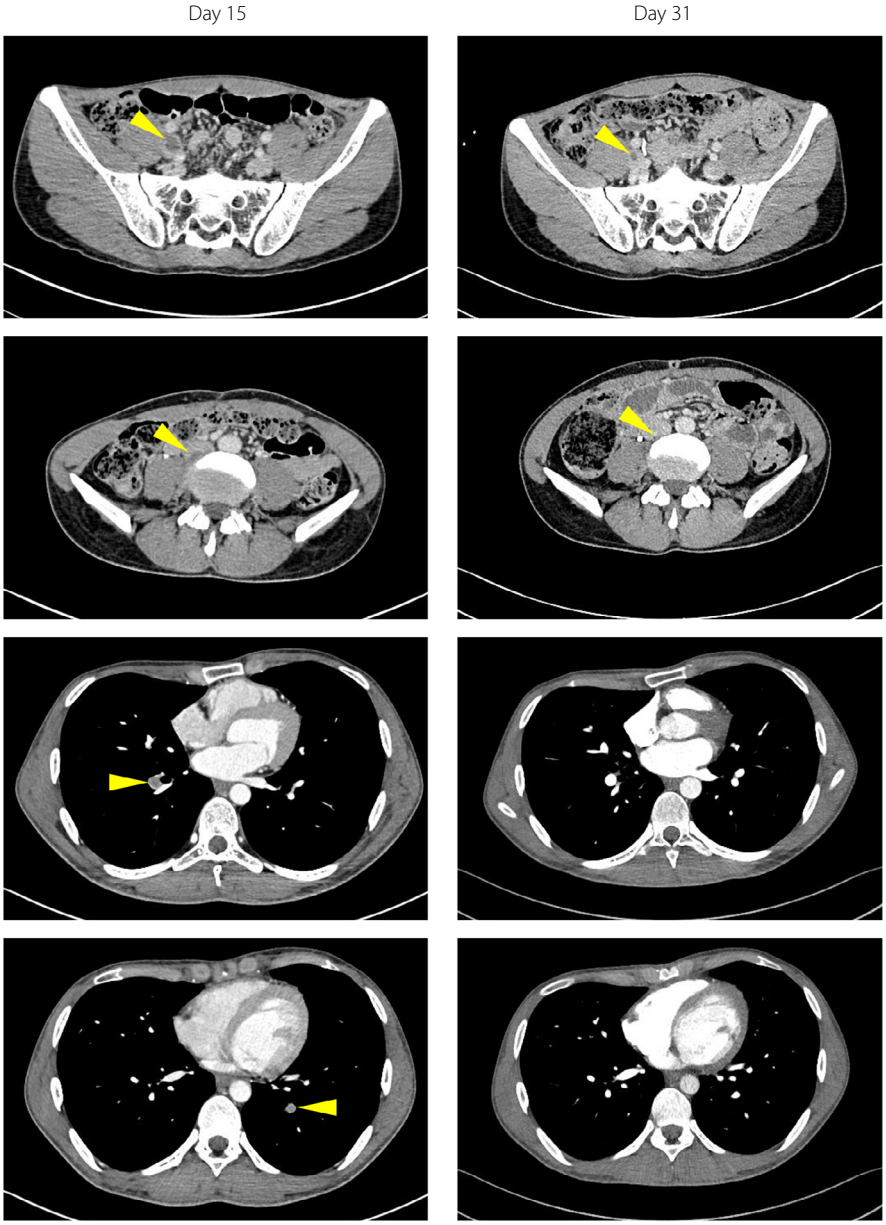

Figure 1 | Contrast-enhanced computed tomography images obtained on days 15 and 31. Yellow arrows indicate the thrombus.

severe PC dysfunction, due to overlapping of the partial PC deficiency and hyperglycemia-induced PC suppression, may have induced the massive DVT with PE. Therefore, we emphasize that strict glycemic control should be the clinical aim in managing patients with both type 1 and type 2 diabetes presenting concomitantly with PC deficiency. Given that the patient had suffered FT1D and would thus be highly prone to hyperglycemia, anti-coagulation therapy should be continued to prevent thrombotic events.

Our present case highlights that venous thrombosis should always be considered as a potential complication of DKA. The prevalence of homozygous PC deficiency is very low (1 in 500,000 to 1 in 750,000 births), while heterozygous PC deficiency is considerably more frequent (1 in 200 to 1 in 500 births). A possible reason for this very low frequency of homozygous PC deficiency is fetal demise and prenatal death[6]. Thus, further loss of PC activity due to hyperglycemia in patients with heterozygous PC deficiency is regarded as being very dangerous. Under DKA conditions, particularly, dehydration and catheterization may increase the risk of thrombosis. On the other hand, as illustrated by our patient, there are cases with partial PC deficiency in whom the condition would not initially

Table 2 | Coagulation-related laboratory results

		Unit	Normal range
D-dimer	0.5 (day 0) 2.5 (day 15) 0.6 (day 32)	μg/mL	0–0.90
Fibrin/fibrinogen degradation products (FDP)	≦2.5 (day 0) 5.9 (day 15) ≦2.5 (day 32)	μg/mL	0–4.90
Protein C activity	46 (day 16) 49 (day 33)	%	64–135
Protein C antigen	41 (day 33)	%	70–150
von Willebrand factor antigen	≧201 (day 16) ≧201 (day 33)	%	50–150
von Willebrand factor activity	196 (day 16) 163 (day 33)	%	50–150
Protein S antigen	89	%	74–132
PT	83.3	%	70.10≦
PT-INR	1.08	INR	≦1.15
APTT	34.4	s	29.6–40.8
Thrombin-antithrombin III complex	3.9	ng/mL	≦3.0
Prothrombin fragment F1 + 2	194	pmol/L	69–229
Antithrombin III	109	%	80–130
Factor II activity	107	%	74–146
Factor X activity	91	%	71–128
Factor XIII antigen	102	%	70–999
Plasminogen	88	%	80–130
Antinuclear antibody	≦1:40	Titer	0–1:79
Anti-cardiolipin antibody	1	U/mL	0–9.9
Anti-cardiolipin β2-glycoprotein I complex antibody	≦1.3	U/mL	0–3.40
Lupus anticoagulant	1	s	0–1.30

be evident due to the absence of any history of thrombosis. Thus, this case suggests the necessity of anti-coagulation therapy combined with acute-phase DKA treatment in patients with PC deficiency, even in those who have been asymptomatic.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: The patient provided written informed consent of this case report.
Registry and the registration no. of the study/trial: September 20, 2022, No. 27404.
Animal studies: N/A.

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