Insulin Resistance and Portal Vein Thrombosis

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Case Presentation

A 76-year-old man with dyslipidemia, hypertension, and type 2 diabetes complicated by coronary artery disease and stage 3 chronic kidney disease was admitted to the hospital with diabetic ketoacidosis (DKA) after a respiratory infection that was treated with antibiotics and glucocorticoids 1 month before admission. His medical history included a motor vehicle accident with perforation of the colon, hemiresection 6 years ago; bladder polyp, resection 5 years ago; and possible bladder cancer, more than 30 years ago. He had no personal or family history of thrombosis.

The patient was diagnosed with diabetes in 2001 and was most recently treated with metformin and sitagliptin. His A1C was maintained at ~7% until 3 years before admission. However, 3 months before admission, his A1C was 10.5%, with no data on glycemic control in the interim 3 years.

He has never smoked, but has a history of heavy alcohol consumption, which he says he stopped 50 years ago. On examination several days after admission, he had a BMI of 27.5 kg/m^2 with central obesity, stable vital signs, clear lung fields, and a benign abdomen.

At admission, he was found to have hyperglycemia with mild anion gap acidosis and elevated beta-hydroxybutyrate. He also had leukocytosis with acute kidney injury (Table 1). The patient's DKA resolved promptly with intravenous (IV) insulin and fluids (Figure 1). He was transitioned to subcutaneous insulin after 24 hours. Despite increasing doses of subcutaneous basal and bolus insulin, his blood glucose remained >300 mg/dL,

TABLE 1. Admission Laboratory Values

Test (Reference Range)	Result
White blood count, K/μL (4.5–11.0)	24.10
Neutrophil, % (NA)	91
Glucose, mg/dL (70–108)	418
Sodium, mg/dL (136–145)	127
Potassium, mEq/L (3.5–5.0)	4.7
Chloride, mEq/L (98–107)	89
Bicarbonate, mEq/L (23–31)	20
Blood urea nitrogen, mg/dL (8–36)	30
Creatinine, mg/dL (0.72–1.25)	1.83
Anion gap, mEq/L (4–12)	18
Calcium, mg/dL (8.4–10.2)	10.5
Phosphorus, mg/dL (2.3–4.7)	3.7
Beta-hydroxybutyrate, mg/dL (0.00–2.81)	25.14
PCO_2, venous, mmHg (38–50)	33
PO_2, venous, mmHg (30–50)	30
pH, venous (7.33–7.43)	7.43
Bicarbonate, venous, mEq/L (24–28)	22

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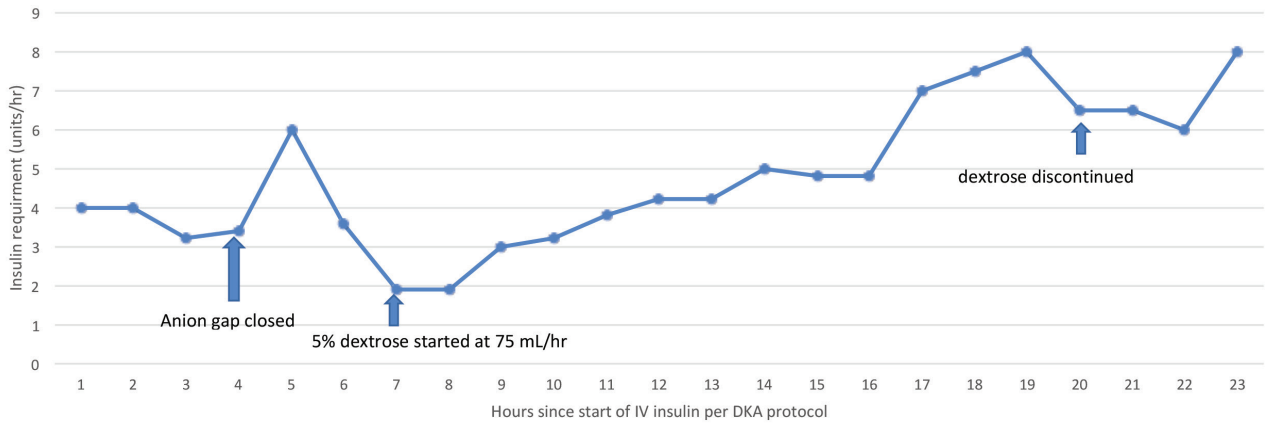

FIGURE 1. Management of DKA with IV insulin during first 24 hours after admission. The patient presented with DKA, which was managed with IV insulin using the DKA Endotool software protocol (Monarch Medical Technologies, Charlotte, N.C.). Anion gap was closed within a few hours after IV insulin was started and remained normal throughout the course. IV dextrose saline was started when blood glucose dropped to <250 mg/dL, according to protocol. Dextrose saline was continued for ~12 hours at a rate of 75 mL/hour and discontinued 2 hours before discontinuation of IV insulin.

ultimately requiring resumption of IV insulin with a requirement of 2–5 units/hour, even when fasting.

Because of elevation of bilirubin and alkaline phosphatase at admission (Table 2), as well as insulin resistance with no obvious cause, abdominal ultrasound imaging was performed. This study showed complete thrombosis of the main, right, and left portal veins. CT scan of the abdomen with contrast confirmed the diagnosis of portal vein thrombosis (PVT) (Figure 2). After excluding the possibility of cirrhosis, the patient was switched from subcutaneous heparin prophylaxis to IV heparin and later bridged to warfarin. Further testing was done to identify the cause of PVT (Table 3).

After transitioning from IV insulin to subcutaneous insulin for the second time, he continued to require up to 1.4 units/kg of subcutaneous insulin daily to maintain glycemic control, despite clinical improvement. Before discharge, his insulin requirement gradually decreased, and he was sent home on a subcutaneous basal-bolus insulin regimen of 60 units daily (0.7 units/kg) (Figure 3). Unfortunately, the patient did not show up for his scheduled outpatient follow-up visit and could not be reached.

TABLE 2. Liver Function Profile

Test (Reference Range)	Result on Admission	Result 3 Days Later
Bilirubin, mg/dL (0.22–1.2)	2.4	1.3
Alkaline phosphatase, units/L (40–150)	174	148
Aspartate aminotransferase, units/L (5–34)	37	48
Alanine aminotransferase, units/L (0–55)	34	47
Protein, total, units/L (6.2–8.1)	10.4	8
Albumin, g/dL (3.2–4.6)	3.5	2.6

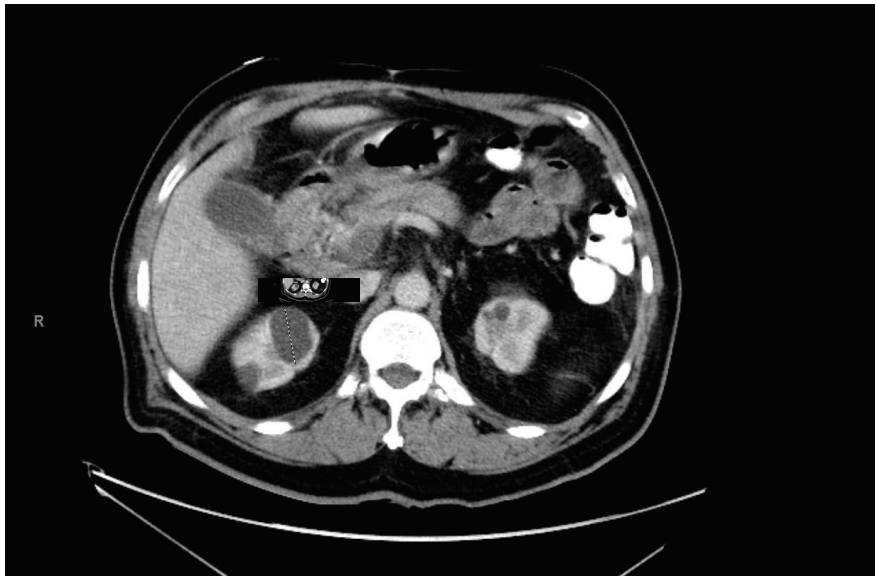

FIGURE 2. CT scan of the abdomen with contrast. Complete thrombosis of main portal vein and right and left portal vein and hepatic branches. There were no abnormalities in liver or ascites. There was no mass or suspicion of malignancy.

TABLE 3. Coagulopathy Profile, Autoimmune Profile, and Tumor Markers

Test	Result
Coagulopathy profile test (reference range)	
International normalized ratio	1.0
Prothrombin time, seconds (9.5–10.9)	10.7
Partial thromboplastin time, seconds (21.5–26.2)	22.8
Antithrombin III, % normal human pooled plasma (75–125)	89
Homocysteine, μmol/L (<11.4)	10.9
Protein C, % (70–180)	83
Protein S, total, % (70–140)	143
Protein S, free, % (57–171)	101
Dilute Russell's viper venom time screen, seconds (≤45)	29
Autoimmune profile test (reference range)	
Antinuclear antibodies (<40)	<40
IgA, mg/dL (101–645)	567
IgG, mg/dL (540–1,822)	1,884
IgM, mg/dL (22–240)	639
Tumor markers test (reference range)	
Carcinoembryonic antigen, ng/mL (<5.0)	2.6
Carbohydrate antigen 19-9, units/mL (<34)	6
Alpha-fetoprotein, ng/mL (<6.1)	1.2

Questions

1. What are the possible explanations for presence of PVT in this patient?
2. What is the connection between insulin resistance and thrombosis, particularly PVT?
3. What are the possible mechanisms of action by which insulin resistance may affect thrombosis?
4. How can PVT affect blood glucose levels?

Commentary

Insulin resistance and hyperinsulinemia have been known to associate with hyperviscosity and thrombosis (1,2). Diabetes, obesity, and metabolic syndrome, in which insulin resistance is the cornerstone of pathogenesis, are established significant risk factors for cardiovascular and peripheral arterial disease (3,4). Furthermore, many studies suggest the association of obesity and metabolic syndrome with venous thromboembolism (5–7). A population-based cohort study showed an increased risk of venous thromboembolism in subjects with increasing insulin resistance, but not independently of BMI (8).

Obesity has been identified as an independent risk factor for PVT in the setting of cirrhosis, which is the most frequent identifiable precipitating factor for PVT (9). Central obesity is associated with noncirrhotic PVT (10). Although obesity is frequently linked to PVT, the association between insulin resistance with a high insulin requirement and PVT has not been reported in patients with noncirrhotic, nontumorous PVT.

PVT has potential severe complications, including variceal bleeding, ascites, hepatic encephalopathy, and cholangitis. Although precipitating factors can be identified in the majority of PVT cases, 30–40% of PVT cases remain of unknown origin (11,12). The leading known local precipitating factor for PVT is cirrhosis; other factors include inflammatory or malignant processes in the abdo-

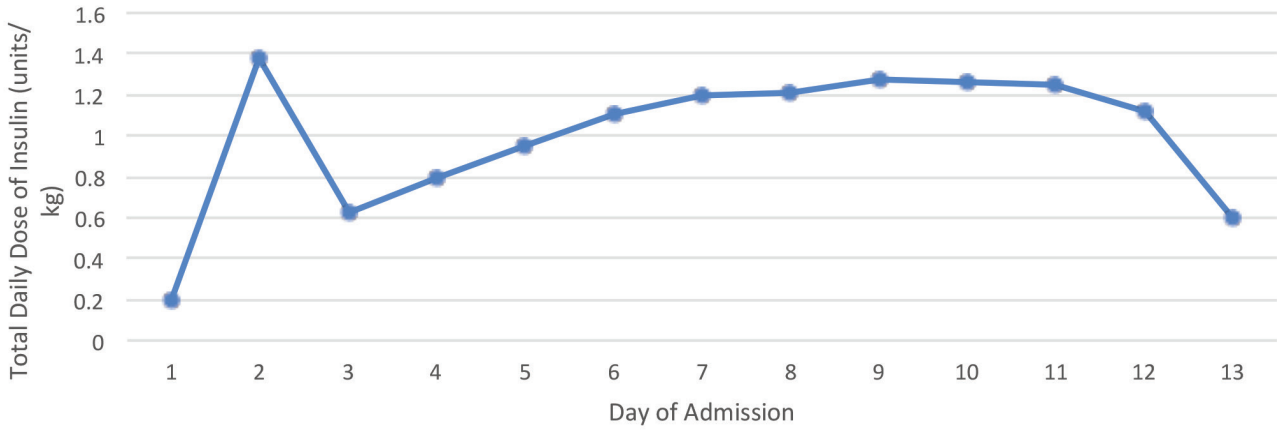

FIGURE 3. Insulin requirement over time. The patient initially needed IV insulin at a high dose and was transitioned to a much lower dose of subcutaneous insulin after resolution of DKA. However, due to his high blood glucose level, IV insulin was started again for a few hours and then transitioned to a relatively higher dose of subcutaneous insulin.

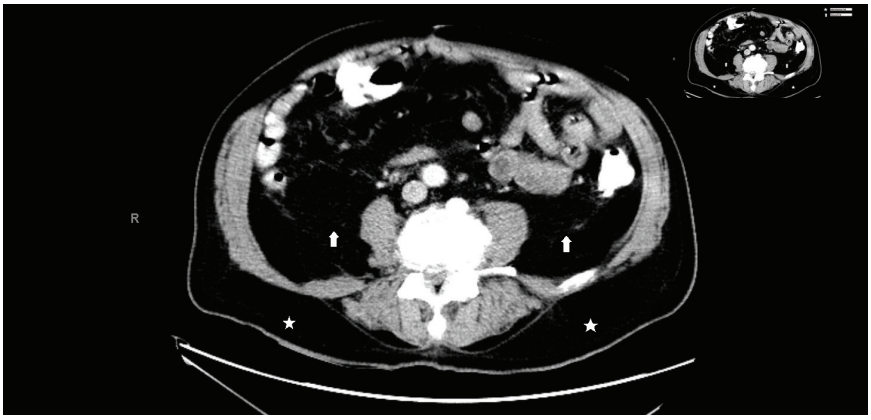

FIGURE 4. CT scan of the abdomen with contrast. Although BMI is only in overweight range, CT showed visceral adiposity with relatively low subcutaneous adiposity. These findings are consistent with insulin resistance.

men, recent trauma or surgical injury, or systemic factors such as hypercoagulopathy and myeloproliferative disorders (13).

In our case, apart from a remote history of heavy alcohol use, there was nothing else on history, exam, or imaging to support cirrhosis. The patient had remote, but no recent, history of trauma or surgery. He had no current or recent evidence of any malignancy or myeloproliferative disorder. Pathology on the biopsy of a bladder polyp performed 5 years ago was benign. Evaluation for underlying coagulopathies was negative. The patient denied smoking, eliminating one of the most common causes for a hypercoagulable state. He did not require any femoral vein catheterization during his hospital course.

However, the patient did have acute hyperglycemia with increased insulin resistance requiring higher insulin doses (Figure 3) on top of baseline insulin resistance with central adiposity (Figure 4). His recent poor glycemic control in the setting of the stress of infection and glucocorticoid use also likely resulted in glucose toxicity, which has been established as a precipitating factor for promoting insulin resistance and inhibiting insulin secretion (14).

There are several mechanisms by which insulin resistance, characterized by hyperglycemia with hyperinsulinemia, may affect thrombosis (15). Platelets of individuals with type 2 diabetes are resistant to the inhibitory effect of insulin on activation and aggregation, making them more susceptible to activation (16). Insulin resistance is associated with low-grade inflammation with resultant oxidative stress. Oxidized LDL cholesterol can enhance platelet-endothelial cell adhesion and release of coagulation factor from glycocalyx, a protective layer covering the vascular wall (17). In vitro, hyperglycemia and hyperinsulinemia increase plasminogen activator inhibitor-1 (PAI-1) expression in vascular smooth muscle cells, which in turns reduces tissue plasminogen activator activity, resulting in decreased fibrinolytic potential (18). Low-grade inflammation also increases circulating levels of interleukin-6, fibrinogen, and tissue factor (TF) expression in vascular cells (19). Hyperglycemia over time disrupts the

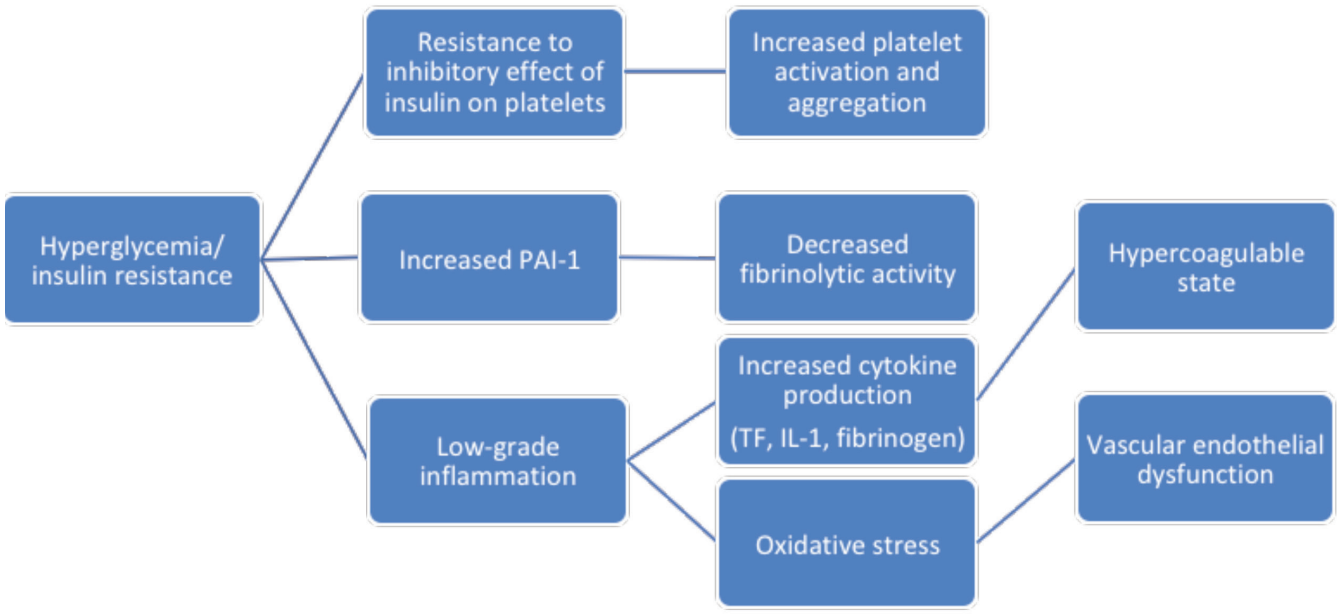

FIGURE 5. Prothrombotic risk in diabetes. IL-1, interleukin-1.

integrity of the vascular wall via deposition of advanced glycosylation end products (19). These effects culminate in vascular endothelial dysfunction and a hypercoagulable state (Figure 5).

Although there are no studies looking specifically at the effect of insulin resistance on PVT, animal studies on nonalcoholic fatty liver disease link insulin resistance to intrahepatic vascular dysfunction (20). On the other hand, in our case, the possibility of idiopathic PVT inducing insulin resistance cannot be excluded. PVT may pose sufficient physiological stress to result in secretion of counterregulatory stress hormones such as catecholamines, cortisol, and cytokines, which in turn can lead to acute hyperglycemia (21). In addition, studies done in cirrhotic patients show that portal hypertension and portosystemic shunting of insulin results in hyperinsulinemia, desensitization, and downregulation of insulin (22). Moreover, rats with partial portal vein ligation, which mimics PVT, were found to have impaired insulin secretion (23).

Clinical Pearls

- In this case, severe hyperglycemia, insulin resistance, and PVT presented simultaneously. It is possible that insulin resistance played a role in the pathogenesis of PVT and that PVT exacerbated insulin resistance.
- Early detection and treatment of PVT reduces mortality and morbidity.
- The signs and symptoms of PVT may be subtle, so there should be a low threshold of suspicion for PVT in patients with insulin resistance.
- Additionally, treatment of insulin-resistant diabetes is important for prevention of arterial and venous thromboembolic complications.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

N.L.A. researched the data and wrote the manuscript. F.J.C. reviewed and edited the manuscript. N.L.A. is the guarantor of this work and, as such, had full access to all the patient data and takes responsibility for the integrity and accuracy of the information presented.

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