Acute coronary thrombosis in a patient with diabetes and severe hyperglycemia

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The pathophysiological processes responsible for acute coronary events in diabetic patients, in addition to the conventional factors associated with plaque rupture, include an enhanced prothrombotic state. This enhanced prothrombotic state results from multiple abnormalities of the coagulation system including platelet activation, impaired fibrinolysis and increased activity of the coagulation cascade. Studies have also demonstrated that severe hyperglycemia can result in an exacerbation of the underlying prothrombotic state, indicating that patients with extreme hyperglycemia are subject to an even greater thrombotic risk. The present case illustrates the thrombotic hazards associated with severe hyperglycemia.

Key Words: Acute coronary syndrome; Diabetes; Prothrombotic state; Thrombus

The case of a man with no history of coronary disease who developed massive thrombosis of his left coronary circulation in the setting of a severe hyperosmolar hyperglycemic state is presented. Although underlying coronary disease likely played a role given the presence of hypertension and type 2 diabetes as atherosclerotic risk factors, the presentation was more likely caused by the prothrombotic state secondary to hyperglycemia as opposed to the more conventional precipitation of thrombosis associated with local plaque rupture. The notion of a widespread hypercoagulable state is supported by subsequent documentation of popliteal artery thrombosis. The present case illustrates the growing body of evidence that recognizes hyperglycemia and insulin resistance as important causes of a prothrombotic state.

CASE PRESENTATION

A 43-year-old man with no history of cardiovascular disease presented with chest pain associated with an altered level of consciousness. The paramedic team reported that the patient had a blood glucose level

Thrombose coronarienne aiguë chez un patient diabétique présentant une hyperglycémie grave

En plus des facteurs classiques associés à la rupture des plaques d'athérome, d'autres processus physiopathologiques sont responsables des accidents coronariens aigus chez les patients diabétiques, entre autres, un état prothrombotique plus marqué. Cet état prothrombotique marqué découle de plusieurs anomalies du système de la coagulation, notamment, activation plaquettaire, fibrinolyse inadéquate et activité accrue de la cascade de coagulation. Des études ont en outre démontré que l'hyperglycémie grave peut exacerber un état prothrombotique sous-jacent, indiquant que les patients présentant une hyperglycémie extrême sont sujets à un risque thrombotique encore plus grand. Le présent cas illustre les risques de thrombose associés à l'hyperglycémie grave.

of 85 mM/L. Fluid resuscitation was started and the patient was taken to the emergency department. The patient arrived at the hospital 40 min after the onset of his symptoms. The initial blood pressure was 100/60 mmHg and his heart rate was 120 beats/min. His breathing was deep and rapid. The point-of-care glucose level was 91 mM/L.

The patient had type 2 diabetes mellitus and hypertension, but no history of cardiovascular disease. Other medical issues included schizophrenia and gastroesophageal reflux disease. Medications before admission included metformin, ramipril and rabeprazole.

There was no elevation of venous pressure, the heart sounds were normal and the lung fields were clear. The electrocardiogram showed sinus tachycardia with ST segment elevation in leads I, aVL and V1 to V6, with associated Q waves compatible with a diagnosis of an extensive ST segment elevation myocardial infarction (Figure 1).

Treatment was initiated with acetylsalicylic acid, clopidogrel and intravenous unfractionated heparin in addition to fluid replacement and intravenous insulin. The patient was taken emergently to the cardiac catheterization laboratory for primary percutaneous coronary

Figure 1) Presenting electrocardiogram with anterolateral ST segment elevation and reciprocal ST segment depression inferiorly

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Figure 2) Left coronary angiogram (right anterior oblique projection – cranial angulation [A] and caudal angulation [B]) showing thrombus in the left main coronary artery and circumflex artery, with abrupt occlusion of the mid left anterior descending and circumflex arteries

intervention with a hospital arrival to first revascularization procedure time of 80 min.

Coronary angiography showed extensive thrombus in both the left main coronary artery and circumflex artery, with abrupt occlusion of the mid left anterior descending and circumflex arteries (Figure 2) and a patent right coronary circulation with no evidence of thrombosis. The left main artery was recanalized using a thrombus extraction catheter. The thrombus was red and appeared fresh. This initial balloon inflation was achieved with a door-to-balloon time of 80 min. Subsequent images revealed total downstream occlusions in both the proximal left anterior descending and circumflex arteries. Repeated attempts to either extract or dilate the occlusions were unsuccessful and the intervention was ultimately abandoned after a procedure time of more than 3 h.

Following the attempted primary angioplasty, the patient was transferred to the coronary care unit for further medical management. Aggressive fluid resuscitation with a total volume of 7.5 L of crystalloid solution was continued with guidance from central hemodynamic measurements with a pulmonary artery catheter. A transthoracic echocardiogram showed severely depressed left ventricular function (left ventricular ejection fraction of 30%), with a dyskinetic anterior wall and septum, and an akinetic lateral wall. The patient's peak troponin I and creatine kinase values were greater than 100 µg/L and 10,936 U/L, respectively.

Subsequent evaluation of right leg pain using Doppler ultrasonography demonstrated a nonocclusive popliteal arterial thrombus. The patient was assessed by the hematology service for a hypercoagulable state, but no underlying thrombophilia was found. With medical management, the patient slowly improved; however, he remained dyspneic with mild exertion.

DISCUSSION

Patients with diabetes are at high risk for myocardial infarction and stroke, with 75% of deaths secondary to cardiovascular complications (1). The proposed pathophysiology to explain the increased risk of cardiovascular events includes endothelial dysfunction and an accelerated rate of atherosclerosis. Both these abnormalities are likely driven by oxidative stress associated with hyperglycemia and insulin resistance (2). However, other factors, such as a prothrombotic state, may also play an important role (1). Studies have shown that patients with diabetes have clotting system abnormalities that result in a chronic hypercoagulable state. Increased platelet activation, increased coagulation and impaired fibrinolysis have all been implicated as playing a role (3). In addition to these chronic prothrombotic modifications, acute changes in blood sugar and insulin resistance have been shown to acutely intensify the hypercoagulable state (1).

Platelet activation represents a key initial step in the hemostatic process. Soluble P-selectin and CD40 ligand, expressed and released into the circulation by platelets during activation, are increased in patients with diabetes (3). Hyperglycemia plays an important role in the increase in platelet activity. An in vitro study (4) demonstrated that glucose resulted in a concentration-dependent increase of adenosine diphosphate-induced platelet activation. The study also observed that increased platelet reactivity was not unique to increased concentrations of D-glucose. Mannitol also increased platelet activation, suggesting that osmotic effects may play an important role (4). Thus, it is possible that patients with markedly elevated glucose levels, as in diabetic ketoacidosis and hyperosmolar hyperglycemia, also have substantially increased platelet reactivity, placing them at a significant risk for thrombosis.

Activation of the coagulation system, indicated by elevated levels of circulating thrombin-antithrombin complexes (TATc) (1), is observed in patients with diabetes. Thrombin represents the final downstream protease of the coagulation cascade and converts fibrinogen into fibrin. Formation of TATc through inhibition of thrombin by antithrombin represents one full cycle through the coagulation pathway and reflects the functional status of the clotting system (1). Patients with diabetes also have increased circulating levels of factors VII, VIII and XI, fibrinogen, von Willebrand factor and tissue factor (1). The mechanism linking diabetes to an increase in clotting system activity remains unclear; however, it is likely mediated through hyperglycemia. When hyperglycemia is induced in healthy patients, TATc and tissue factor levels are doubled over a period of hours (5). It has been suggested that advanced glycation end products may also be responsible for increased tissue factor expression (2).

Impaired fibrinolysis, due to elevated levels of plasminogen activator inhibitor type 1 (PAI-1), further contributes to a hypercoagulable state in patients with diabetes (3). PAI-1 inhibits the conversion of plasminogen into plasmin and consequently reduces fibrinolytic activity (3). An in vivo study in healthy volunteers using a hyperinsulinemic-euglycemic clamp, demonstrated a 2.5-fold increase in levels of PAI-1 relative to baseline (5). This study suggested that impaired fibrinolysis in patients with diabetes is mediated by hyperinsulinemia rather than

hyperglycemia. Hyperinsulinemia increases PAI-1 levels by stabilization of the PAI-1 messenger RNA transcript through the actions of insulin and insulin-like growth factor type 1 (3). Adipocytes have been found to be a major source of PAI-1, providing a direct link between obesity and a suppressed fibrinolytic system (3). Finally, inflammatory cytokines such as transforming growth factor-beta and tumour necrosis factor-alpha – both of which are believed to have important roles in the metabolic syndrome – increase the release of PAI-1 from adipose tissue (3).

The promotion of a prothrombotic state is one important factor responsible for the increased burden of vascular disease and thrombotic events in diabetic patients. Basic science research has begun to unravel the pathophysiological mechanisms relating insulin resistance, hyperglycemia and thrombosis. Current information suggests that all aspects of the clotting system are modified in diabetes, resulting in an enhanced risk for thrombosis. The present case illustrates how acute exacerbations of hyperglycemia, such as those that occur in diabetic ketoacidosis and the

hyperosmolar hyperglycemic state, can further aggravate the hypercoagulable state, placing affected patients at significant thrombotic risk.

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