Empagliflozin-Associated Pancreatitis: A Consideration for SGLT2 Inhibitors

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ABSTRACT
Empagliflozin belongs to a class of sodium-glucose cotransporter-2 inhibitors, a medication approved by the US Food and Drug Administration in 2014 for the treatment of type 2 diabetes mellitus. Well-known side effects of this medication include symptomatic hypotension, hypoglycemia, and urinary tract infections among others. We present a case of severe epigastric abdominal pain consistent with acute pancreatitis in the setting of empagliflozin use, suggesting a possible drug-induced acute pancreatitis.

INTRODUCTION
Empagliflozin is a drug in the new class of diabetic medications sodium-glucose cotransporter-2 (SGLT2) inhibitors, indicated for treating type 2 diabetes mellitus. The mechanism of action of empagliflozin is to reduce renal reabsorption of glucose and increase its urinary excretion.1 Well-known side effects of this class of medications include symptomatic hypotension through the drug’s ability to cause intravascular volume contraction, hypoglycemia when used with insulin, urinary tract infections, and mycotic infections such as vulvitis and vulvovaginal candidiasis.1 In the review of the current literature, although rare in occurrence (less than 0.1%), drug-induced acute pancreatitis (DIAP) should be considered an adverse effect in patients treated with SGLT2 inhibitors. DIAP is a rare entity, with more than 500 drugs being listed as having DIAP as an adverse effect by the World Health Organization and more than 180 drugs have been implicated to directly cause DIAP.2,3 To our knowledge, there are very few reported cases of empagliflozin-induced pancreatitis.4,5 In addition, canagliflozin, an SGLT2 inhibitor, is known to rarely cause pancreatitis with an incidence 1%.6–10 We report a case of a 47-year-old man who presented with severe epigastric abdominal pain found to have DIAP in the setting of empagliflozin use.

CASE REPORT
A 47-year-old man with a history of abdominal aortic aneurysm status after stent placement, hypertension, and type 2 diabetes mellitus presented with a complaint of severe, epigastric abdominal pain associated with nausea and vomiting for 2 days duration. The patient denied a history of pancreatitis, consuming alcohol, narcotic use, recent trauma, surgical procedures, or exposure to venomous animals. The patient was admitted for management of pancreatitis. Social history including was negative for smoking history, alcohol ingestion, illicit drug use, or cannabis use. His home medications included empagliflozin (initiated 2 months before), atenolol, and hydrochlorothiazide (HCTZ). He had no known significant family history.

On admission, the patient’s vital signs were within normal limits. Physical examination was significant for epigastric tenderness without organomegaly and absence of skin rash or scleral icterus. Laboratory workup revealed an elevated lipase of 220 mg/dL. Other laboratory findings were unremarkable, including the absence of eosinophilia, triglyceride level of 123 mg/dL (drawn fasting 1 day after admission), normal electrolyte levels, and liver function tests. Abdominal computed tomography angiography was obtained to evaluate the aortic stent and the pancreas, which revealed fat stranding and findings consistent with pancreatic inflammation located within the head of the pancreas (Figure 1). The gall bladder was unremarkable on abdominal ultrasound without evidence of cholelithiasis or other intraabdominal processes.
The patient was treated with conservative management, including intravenous hydration and pain management. Empagliflozin was held because of suspicion of pancreatitis caused by this medication because of the absence of other inciting causes. The patient was subsequently discharged after 2 days and instructed to discontinue empagliflozin along with follow-up with his primary care physician. The patient refused endoscopic ultrasound. The patient has not had any further episodes of pancreatitis or gastrointestinal complaints at the 2-month outpatient follow-up.

DISCUSSION

The true incidence of DIAP is unknown because there are few population-based studies available, and the quality of available evidence is limited. Although gallstones (35%–40% of cases) and alcohol use (30% of cases) are considered the most common causes of acute pancreatitis, other causes are extensive and include idiopathic pancreatitis, genetic causes among others. In recent literature, the PRSS1, SPINK1, CFTR, CTRC, and CASR genetic variants have been confirmed as chronic pancreatitis-associated genetic factors.

Empagliflozin is a relatively new diabetic medication in the class of SGLT2 inhibitors, with very few case reports describing its known potential for causing pancreatitis. Badalov et al created a classification system that assesses the likelihood that certain drugs are associated with DIAP; the classifications are based on the number of case reports, rechallenge data, consistent latency period, and the ability to exclude other causes of AP. Based on the Badalov classification, empagliflozin would be characterized as Class III with at least 2 case reports published without rechallenge data or a consistent latency period. We implemented the use of the Adverse Drug Reaction Probability Scale—a method by which to assess whether there is a causal relationship between an identified clinical event and a drug; scores range from −4 to +13 and interpreted to reflect the strength of the causal relationship.

Our patient received a score of 6—further supporting the temporal relationship between empagliflozin therapy and DIAP. He, all other likely causes of pancreatitis, were ruled out. The likelihood of HCTZ causing our patient’s pancreatitis is unlikely because he had been on this medication without complications for many years before presentation. Our patient also did not present with hypercalcemia or hypertriglyceridemia, which are the assumed mechanisms of HCTZ-induced pancreatitis. In reviewing a recent case report by McIntire and Bayne, empagliflozin-induced pancreatitis occurred at day 104. As mentioned above, our patient had been started on empagliflozin therapy approximately 60 days before presentation. We believe that this timeframe further supports the likelihood of a causal relationship. A drug rechallenge is defined as the readministration of a suspected drug that had been previously withdrawn; this may provide valuable information to assess causality between the medication and the reaction. This case demonstrates that SGLT2 inhibitors, although a rare cause, should be considered an important part of a clinician’s differential when other common etiologies of pancreatitis have been excluded.

Our case emphasizes the importance of the general gastroenterologist and clinician increased awareness of new classes of diabetic medications, especially, but not limited to empagliflozin within the class of SGLT2 inhibitors and their untoward side effects of acute pancreatitis. The clinician should be cognizant that certain medications have more robust evidence than others to associate the drug to DIAP. Larger case-control studies on DIAP are needed to study the true potential these drugs.

DISCLOSURES

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