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Tudor Sturzoiu, MD
*Thomas Jefferson University*, tudor.sturzoiu@jefferson.edu

Sameep Thapa, MD
*Thomas Jefferson University*, sameep.thapa@jefferson.edu

Ellen Solomon
*Thomas Jefferson University*, ellen.solomon@students.jefferson.edu

Suchit Bhutani, MD
*Thomas Jefferson University*, suchit.bhutani@jefferson.edu

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A Case of Acute Pancreatitis Associated with Empagliflozin

Tudor Sturzoiu MD\textsuperscript{1}, Sameep Thapa, MD\textsuperscript{1}, Ellen Solomon\textsuperscript{2}, Suchit Bhutani, MD\textsuperscript{1}

1. Department of Medicine, Thomas Jefferson University, Philadelphia, PA
2. Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA

ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are being prescribed increasingly more often for type 2 diabetes mellitus as well as heart failure. They have not typically been associated with acute pancreatitis, but there has been a steady flow of case reports implicating them in acute pancreatitis over the years since they were initially approved. Here, we present the case of an 82-year-old woman with a past medical history of T2DM, COPD, hyperlipidemia, a remote stroke, peripheral arterial disease, and remote breast cancer now with recurrent localized breast cancer on treatment with ademaciclib and letrozole who presented to the emergency department with abdominal pain, weakness, decreased oral intake, and nausea and vomiting. These symptoms started two weeks after the initiation of the SGLT-2 inhibitor empagliflozin for her T2DM. Initial labs were notable for sodium of 129, glucose of 409, a normal anion gap, beta hydroxybutyrate of 4.6, serum creatinine of 0.92, calcium of 9.8, total bilirubin of 3.0 with direct bilirubin 2.6, alkaline phosphatase of 773, AST of 330, ALT of 446, lipase of 1,159, triglycerides of 237, and leukocyte count of 4.9. Following admission, CT and MRCP demonstrated pancreatitis with no intrahepatic or extrahepatic ductal dilation, gallstones choledocholithiasis, or other obvious etiology of her presentation. Her symptoms improved with supportive care following the discontinuation of her SGLT-2 inhibitor and she was discharged to inpatient rehab shortly after presentation. This case highlights the importance of keeping the uncommon diagnosis of SGLT-2 inhibitor associated pancreatitis in mind in patients who present with acute pancreatitis.

INTRODUCTION

According to the Centers for Disease Control, the prevalence of type 2 diabetes mellitus (T2DM) in 2020 was nearly 10.5\%\textsuperscript{1}. Given its overall burden and the range of complications that can arise from long-term T2DM, it makes sense that there continue to be emerging therapies to treat it. One of the drug classes approved within the last decade, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, function by reducing the reabsorption of glucose at the level of the renal tubule, thus causing lower blood glucose levels through therapeutic glucosuria. It has been increasingly prescribed for T2DM and was recently approved for the treatment of heart failure with reduced ejection fraction even in the absence of T2DM. Pancreatitis, which has been associated with some classes of T2DM medications, is an uncommon side effect of SGLT-2 inhibitors. Still, there have been a few reports of SGLT-2 inhibitors induced pancreatitis since their approval, and it is important to keep this side effect in mind when prescribing these drugs for the first time or when treating someone for acute pancreatitis in the setting of recent initiation of an SGLT-2 inhibitor\textsuperscript{2-4}.

Here, we present the case of an 82-year-old woman who presented with subacute abdominal pain caused by pancreatitis 30 days after initiation of the SGLT-2 inhibitor empagliflozin in the setting of poorly controlled diabetes.

CASE REPORT

Our patient is an 82-year-old woman who presented to the emergency department in January of 2021 with almost 2 weeks of abdominal pain with radiation to her back, weakness, and decreased oral intake. She had also been experiencing nausea and vomiting for 3-4 days prior to admission. Her significant past medical history included poorly controlled T2DM with recent Hgb-A1C of 11.1\%, COPD, a remote stroke, hyperlipidemia, peripheral artery disease, and two previous episodes of breast cancer in 1994 and 2015 now with recurrence. Her medications included metformin, fluticasone/salmeterol, tiotropium, albuterol, rosuvastatin, clopidogrel, lorazepam, abemaciclib and letrozole. She was initiated on empagliflozin to optimize the treatment of her T2DM on at the start of December of 2020. Additionally, she was recently diagnosed with recurrent estrogen receptor positive, progesterone receptor positive, human epidermal growth factor receptor-2 negative inflammatory breast cancer of the right breast in November of 2020, at which time she was initiated on abemaciclib and letrozole.
On presentation, initial vital signs included a temperature of 96.6°F, pulse of 83 beats per minute, blood pressure of 156/75 mmHg, respiratory rate of 18, and oxygen saturation of 96% on room air. Physical examination was significant for lethargy, dry mucous membranes, diffuse abdominal tenderness without rebound or guarding, and a firm right breast mass with dimpling of the overlying skin. Initial labs were notable for a sodium of 129, bicarbonate of 15 (baseline 18-20) with a normal anion gap, serum creatinine of 0.92, glucose of 409, calcium of 9.8, total bilirubin of 3.0 with direct bilirubin 2.6, alkaline phosphatase of 773, AST of 330, ALT of 446, beta hydroxybutyrate of 4.6, lactate of 1.4, lipase of 1,159, triglycerides of 237, leukocyte count of 4.9, and hemoglobin of 11.3. CT of the abdomen and pelvis was normal liver, normal bile ducts without dilation, and a normal gallbladder without gallstones. She had held most of her medications on her own prior to presentation due to a concern that they could be related to her symptoms. The following day, ultrasound of the abdomen confirmed absence of cholelithiasis and choledocholithiasis with normal caliber intrahepatic and extrahepatic biliary ducts including the common bile duct as well as a normal gallbladder without stones or edema. It also showed signs of acute pancreatitis, though this was better imaged on the CT scan from the prior day. Due to concern for an occult obstructive lesion in the biliary system in the setting of persistently high ALP, AST, ALT, and bilirubin in the setting of malignancy, she was sent for magnetic resonance imaging with MRCP, which demonstrated no intrahepatic or extrahepatic biliary ductal dilatation and again confirmed no cholelithiasis or choledocholithiasis. It also visualized a 0.7 cm intraductal papillary mucinous neoplasm, which was slightly increased in size since the last time it was imaged in 2012. At this point, her symptoms had improved significantly since her SGLT-2 inhibitor was held, but her liver function tests (LFTs) were persistently elevated. As such, she underwent esophagogastroduodenoscopy with endoscopic ultrasound, which showed diffuse thickening of common hepatic duct and common bile duct walls without dilation or stones. In consultation with GI, it was determined that her persistently elevated LFTs were in the setting of acute pancreatitis, and they were expected to trend down over the next days to weeks. The patient continued to improve symptomatically, and her LFTs did trend down before her eventual discharge to inpatient rehabilitation.

DISCUSSION

SGLT-2 inhibitors have been implicated in drug-induced pancreatitis in a few case reports4-6. A recent review aggregated case reports of SGLT2-associated pancreatitis and found that four reports were associated with canagliflozin, two with empagliflozin, and one with dapagliflozin3. Since that paper was published, another case report for empagliflozin-induced pancreatitis has been published4. Our case report is the fourth that we were able to find for empagliflozin. In the previous review, the mean time interval from initiation of the SGLT-2 inhibitor to diagnosis of pancreatitis was 39 days, which falls in line with the time interval observed in this case – 30 days.

Our patient presented with clinical, laboratory and imaging findings of acute uncomplicated pancreatitis. In the absence of any of the other classic causes of pancreatitis (including alcoholism, gallstones, obstructive mass lesion in the setting of malignancy, and hypertriglyceridemia) and the recent initiation of an SGLT-2 inhibitor, we believe drug-induced pancreatitis to be the most likely cause of her presentation. Letrozole and abemacencil were also recently initiated, but these are less likely to be causes of pancreatitis. We were not able to find any case reports of pancreatitis associated with these two agents, and in fact, letrozole has been prescribed as an alternative to tamoxifen in a number of cases where tamoxifen was implicated in pancreatitis6-7.

The mechanism for the development of pancreatitis is unknown with regards to this drug class, which has only been associated with pancreatitis in a few case reports. It is becoming more apparent that SGLT-2 inhibitors have broader in vivo actions than just SGLT-2 inhibition in renal tubular cells, and it is possible that some of these effects are responsible for the development of pancreatitis. The range of conditions for which SGLT-2 inhibitors are approved is expanding, such that they will be prescribed increasingly more commonly over the next years, which could lend further insight into the extent of their physiologic actions.

This case report highlights the importance of keeping the rather uncommon diagnosis of SGLT-2-induced pancreatitis in mind when treating a patient with acute pancreatitis, as timely discontinuation of the SGLT-2 inhibitor caused improvement of symptoms in all case reports that we reviewed.
REFERENCES


“Not fragile like a flower, fragile like a bomb” – Heping Sheng, MD