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EMPAGLIFLOZIN-INDUCED LIVER INJURY

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ABSTRACT

Background: Drug-induced liver injury is an uncommon, idiosyncratic adverse reaction with heterogeneous clinical presentations, ranging from asymptomatic transaminase elevations to acute liver failure. Sodium-glucose cotransporter 2 inhibitors, widely prescribed for type 2 diabetes due to their glycaemic, cardiovascular, and renal benefits, are generally considered safe to the liver. Nonetheless, rare cases of cholestatic and hepatocellular drug-induced liver injury have been reported, highlighting the need for vigilance and systematic evaluation when liver dysfunction occurs in patients receiving these agents.

Case report: We describe a 56-year-old man with type 2 diabetes and chronic schizophrenia who developed cholestatic liver injury 36 days after initiating empagliflozin 10 mg od. The patient presented with jaundice, dark urine, and pale stools, with laboratory findings revealing elevated bilirubin, gamma-glutamyl transferase, and alkaline phosphatase disproportionate to alanine aminotransferase. Comprehensive work-up excluded viral, autoimmune, metabolic, and obstructive causes. Imaging confirmed intrahepatic cholestasis without biliary obstruction. Causality assessment using the Roussel Uclaf Causality Assessment Method, Maria and Victorino and Naranjo scores indicated probable adverse drug reaction. Liver biopsy demonstrated acute cholestatic injury with portal inflammatory infiltrates and ductular reaction, consistent with drug-related pathology. Empagliflozin withdrawal led to gradual clinical and biochemical recovery.

Conclusion: Empagliflozin can, in rare cases, trigger idiosyncratic cholestatic drug-induced liver injury, even in patients with cirrhosis. Early recognition, prompt drug withdrawal, and systematic evaluation are essential. This case adds to the limited literature on sodium-glucose cotransporter 2 inhibitor-associated hepatotoxicity.

KEYWORDS

Drug-induced liver injury, empagliflozin, sodium-glucose cotransporter 2 inhibitor, cholestatic hepatitis, idiosyncratic hepatotoxicity

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LEARNING POINTS

- Drug-induced liver injury is a diagnosis of exclusion. Clinicians must rule out other causes, especially biliary obstruction, and use structured causality assessment tools to identify the offending drug.
- Empagliflozin and other sodium-glucose cotransporter 2 inhibitors can, in rare cases, cause liver injury. Monitoring liver function after initiating these drugs is advisable, particularly in patients with pre-existing liver disease.
- There is no specific treatment for idiosyncratic drug-induced liver injury. Prompt withdrawal of the offending and supportive care are usually sufficient for recovery.

INTRODUCTION

Drug-induced liver injury (DILI) is an uncommon, idiosyncratic adverse reaction to medications that can occur weeks to months after initiation[1-6]. It is unpredictable and may present as hepatocellular, cholestatic, or mixed injury, depending on the site of hepatocyte or bile duct damage[2-5]. Clinical manifestations range from asymptomatic liver enzyme elevations to jaundice, pruritus, malaise, or acute liver failure[2-5]. Diagnosis is challenging due to the lack of specific biomarkers and relies on clinical suspicion, temporal association with drug exposure, and exclusion of other causes such as viral hepatitis, autoimmune liver disease, metabolic disorders, and biliary obstruction[1-6]. Structured causality assessment tools, including Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM), Maria and Victorino (M&V) and Naranjo scores, are recommended to support diagnosis[3,6,7].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, are widely used for type 2 diabetes due to glycaemic, cardiovascular and renal benefits[8]. Although generally safe for the liver, rare cases of cholestatic DILI have been reported with SGLT2 inhibitors[9-11]. Dapagliflozin has been associated with acute cholestatic hepatitis in patients with non-alcoholic steatohepatitis -related cirrhosis[11], and empagliflozin-related cases include acute hepatitis in non-alcoholic fatty liver disease (NAFLD)[9] and cholestatic liver injury after 1 month of therapy[10]. Mechanisms are thought to involve immune-mediated reactions, genetic predisposition, and environmental factors[1-5].

We describe the case of a 56-year-old man with type 2 diabetes who developed cholestatic drug-induced liver injury approximately 1 month after initiation of empagliflozin.

CASE DESCRIPTION

A 56-year-old man with type 2 diabetes and paranoid schizophrenia, treated with metformin and sitagliptin, clozapine, trihexyphenidyl, and diazepam, presented with a 2-week history of nausea and vomiting, dark urine and pale stools, during the preceding week. Other than initiation of empagliflozin 10 mg od, 36 days prior, the patient denied any recent medication changes, alcohol use, illicit substances, or supplement use.

On physical examination, he was somnolent, dehydrated, and diffusely icteric, with a non-tender abdomen and palpable hepatomegaly, without asterixis or other stigmata of chronic liver disease. No cardiopulmonary abnormalities, peripheral oedema, or signs of phlebothrombosis were noted.

Laboratory evaluation revealed normocytic normochromic anaemia (Hb 11.3 g/dl) with normal leukocyte and platelet counts, marked liver biochemistry abnormalities: alanine aminotransferase (ALT) 258 U/l, aspartate aminotransferase 149 U/l, total bilirubin 17.6 mg/dl, gamma-glutamyl transferase (GGT) 785 U/l, alkaline phosphatase 366 U/l, consistent with a cholestatic pattern. Inflammatory markers, albumin, lactate dehydrogenase, coagulation parameters, and renal function were within normal limits. Extensive work-up excluded alternative aetiologies: viral serologies (hepatitis A, B, C or E, human immunodeficiency virus, cytomegalovirus, herpes simplex virus-1/2 and Epstein-Barr virus) and autoimmune markers (antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies and anti- liver-kidney microsomal antibodies) were negative, and metabolic and infiltrative causes were ruled out. Abdominal computed tomography (CT) scan demonstrated hepatomegaly (260 mm) with heterogeneous parenchymal texture, a non-specific lesion in segment III, gallbladder wall thickening with pericholecystic fluid but no calculi or biliary ductal dilation, and splenomegaly (160 mm). Contrast-enhanced imaging revealed oedema of the porta hepatis and gallbladder wall without evidence of extrahepatic biliary obstruction, effectively excluding acute cholecystitis or choledocholithiasis, and indicating intrahepatic cholestasis.

Empagliflozin was promptly discontinued. Causality assessment using the CIOMS/RUCAM scale yielded a score of 6, the M&V score was 15, and the Naranjo score was 7, all consistent with probable drug-induced liver injury. Percutaneous liver biopsy on day 10 of admission revealed moderate acute cholestatic injury, with hepatocellular cholestasis and portal inflammatory infiltrates, supporting a drug-related aetiology.

Of note, the patient also developed severe hyperlipidaemia concomitant with the drug-induced liver injury, a phenomenon considered related to the hepatic event, and nosocomial *Pseudomonas aeruginosa pneumonia*, which was successfully treated with piperacillin–tazobactam without complications and with clinical and laboratory improvement. The patient was discharged on day 34 with marked improvement in cholestatic liver biochemistry. He was advised to avoid empagliflozin and scheduled for follow-up

appointments in internal medicine and psychiatry.

DISCUSSION

This case illustrates idiosyncratic DILI triggered by empagliflozin. Idiosyncratic DILI is a spectrum of unpredictable liver injuries occurring in a minority of exposed individuals. It often has an immune-mediated basis (linked to HLA genotypes)[2,3,5]. In practice, almost any drug can cause DILI, so new or recently started medications (including SGLT2 inhibitors) must be scrutinized[3-5]. Here, empagliflozin was the only recent change. Other medications (clozapine, metformin, sitagliptin) had been long-standing without prior liver issues. Metformin is not known for hepatotoxicity, and clozapine-induced liver injury typically presents earlier or with different features[3,4,6]. The timing (36 days after empagliflozin initiation), the cholestatic pattern, and the biopsy findings point to empagliflozin as the culprit[6,10,11].

Several aspects reinforce the diagnosis: the latency period fits idiosyncratic DILI (usually days to months after starting a drug)[2,3,5]. The high bilirubin and GGT with disproportionately mild ALT suggest a cholestatic phenotype[6]. In cholestatic DILI, alkaline phosphatase(ALP) or GGT is markedly elevated relative to ALT[6]. According to European Association for the Study of the Liver (EASL) criteria, a cholestatic pattern is defined by ALP ≥2× upper limit normal or ALT/ALP ratio ≤2 (our patient meets this)[6]. Imaging ruled out obstruction, fulfilling guideline criteria for intrahepatic DILI[6]. CIOMS/RUCAM, M&V and Naranjo scoring supported probable causality, and liver biopsy confirmed cholestasis with features (portal fibrosis, ductular reaction) typical of drug injury[6,7,10,11].

Although empagliflozin has a good safety profile, clinicians should recognize that hepatic injury is possible[8-11]. In pooled trials, dapagliflozin and empagliflozin had similar liver event rates as placebo, but isolated post-marketing cases have emerged[8-11]. Levine et al. reported a case of cholestatic hepatitis in a cirrhotic woman on dapagliflozin[11], and Famularo et al. described acute hepatitis in an NAFLD patient on empagliflozin[9]. Nunes et al. reported a 70-year-old who developed cholestatic DILI 1 month after initiation empagliflozin, with biopsy confirmation and full recovery upon withdrawal[10]. These reports, together with our case, indicate that empagliflozin can, in rare cases, trigger DILI; and our report adds evidence and highlights that even patients without overt cirrhosis may be affected[9-11].

Liver biopsy in our patient showed predominantly cholestatic injury. This aligns with published cases; for instance, the dapagliflozin biopsy showed portal fibrosis, ductular reaction and cholestasis[11]. Such histology underscores drug toxicity rather than other aetiologies. Notably, Nunes et al found portal-based fibrosis and cholestasis as well[10]. In general, histology in DILI can vary, but features like bile duct injury and cholestasis support the diagnosis[2-5].

Management of idiosyncratic DILI is largely supportive. Immediate withdrawal of the offending drug is crucial[6]. There is no specific antidote for idiosyncratic DILI, unlike acetaminophen toxicity[1]. After drug cessation, most patients gradually improve[6,10,11]. Close monitoring is needed to ensure resolution and to detect chronic injury[6]. In rare fulminant cases, transplantation may be required, but our patient recovered without progression to liver failure[6,10,11].

In summary, this report adds to the limited literature on empagliflozin-induced DILI. It underscores that DILI can occur with modern diabetes drugs and highlights the importance of a systematic evaluation (including imaging and/or eventual biopsy) to confirm the diagnosis[6,10,11]. Awareness of this potential adverse effect can lead to prompt identification and management[6,9-11].

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