CASE REPORT

PERSISTENT HEPATOCELLULAR SECRETORY FAILURE: A RARITY IN HEPATOLOGY

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Persistent hepatocellular secretory failure (PHSF) is a rare condition that presents as elevated bilirubin despite treatment and elimination of all possible causes, including intrahepatic and extrahepatic biliary obstruction. Very limited literature is available regarding this condition, highlighting its rarity. A 65 years old male who was diagnosed with symptoms of cholestasis. He was diagnosed with pancreatic adenocarcinoma leading to obstructive jaundice. He underwent endoscopic retrograde cholangiopancreaticography and self-expandable metallic stent (SEMS) placement in the common bile duct. Despite SEMS placement, he complained of persistent jaundice, pale stools and itching. His bilirubin was persistently elevated and imaging showed patent stent. After a thorough work-up and discussion in a multidisciplinary team meeting, he was diagnosed as a case of PHSF. The patient is being managed conservatively with ursodeoxycholic acid and cholestyramine. His liver function tests improved after addition of rifampin.

Keywords: Obstructive Jaundice; Hyperbilirubinemias; Endoscopic Retrograde Cholangiopancreatography

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INTRODUCTION

Persistent hepatocellular secretory failure (PHSF) is a rare condition marked by ongoing liver damage, potentially fatal without transplantation. It's triggered by factors like toxins, medications, or temporary biliary obstruction, leading to elevated biochemical markers even after the initial cause is removed. In a study, patients with severe PHSF were identified, and rifampin, a Pregane X Receptor (PXR) agonist, was used as a possible treatment regimen.[1] There are few real-world studies on rifampin in cholestasis, particularly in patients with severe jaundice.[2] There is very limited literature available on Persistent Hepatocellular secretory failure, which highlights its rarity.

Here, we report a case of persistent hepatocellular secretory failure, in which serum bilirubin level was increased despite the elimination of all potential risk factors for hepatocellular damage. We sought to increase our understanding of persistent hepatocellular secretory failure, its aetiology and its treatment.

CASE SUMMARY

A 65-year-old businessman with no previous comorbidities presented with complaints of pale stool, dark urine and pruritus. Our patient reported a weight loss of 10kgs over the past 3 months. His past medical and surgical history was unremarkable. Family history was positive for night blindness in daughters, lung carcinoma in brother and hepatocellular carcinoma in father. There was no history of alcohol and drug abuse, or exposure to any toxins. On physical examination, there was jaundice, temporal wasting and palpable gall bladder. His initial lab work showed, total bilirubin 25.98 mg/dl (normal up 1.2 mg/dl), direct bilirubin 23.02 mg/dl (normal up to 3.0 mg/dl), alkaline phosphatase 340 U/L (normal up to 40-130 U/L), Gamma Glutamyl transferase 60 U/L (normal up to 60 U/L), aspartate transaminase 86 U/L (normal up to 40 U/L) and alanine transaminase 90 U/L (normal up to 41 U/L).Contrast enhanced CT scan was performed which revealed a 39×37×42 mm hypodense lesion in head of pancreas and uncinate process with upstream moderate dilation of pancreatic duct and encasement of superior mesenteric vein along with local infiltration of pylorus and medial duodenal wall. (Figure 1a)

Endoscopic retrograde cholangiopancreaticography(ERCP) was performed. Cholangiogram showed dilated proximal biliary channels, with tight distal common bile duct stricture in the pancreatic head. (Figure 1b). A 10×60 mm fully covered self-expandable metallic stent (SEMS) was placed, establishing drainage. Endoscopic ultrasound was performed, and a fine needle biopsy of the pancreatic head mass was conducted, revealing a moderately differentiated adenocarcinoma of pancreaticobiliary origin.

Post procedure, his total bilirubin was 27.28 mg/dl (normal up to 1.2 mg/dl), gamma GT 74 U/L

(normal up to 60 U/L) and alkaline phosphatase 332 U/L (normal 40-130 U/L). His symptoms improved and the patient was subsequently discharged. 3 weeks later, he presented again with complaints of persistent jaundice and vomiting. The patient underwent a CT scan, which confirmed the stent was still patent. Despite patent stent, his bilirubin remained persistently high. Through extensive investigation, all possible causes of cholestasis were ruled out, and the diagnosis of persistent hepatocellular secretory failure was made. Patient was started on rifampin 300 mg once daily and his bilirubin decreased at a rate of approximately 0.75 mg/dl/day.

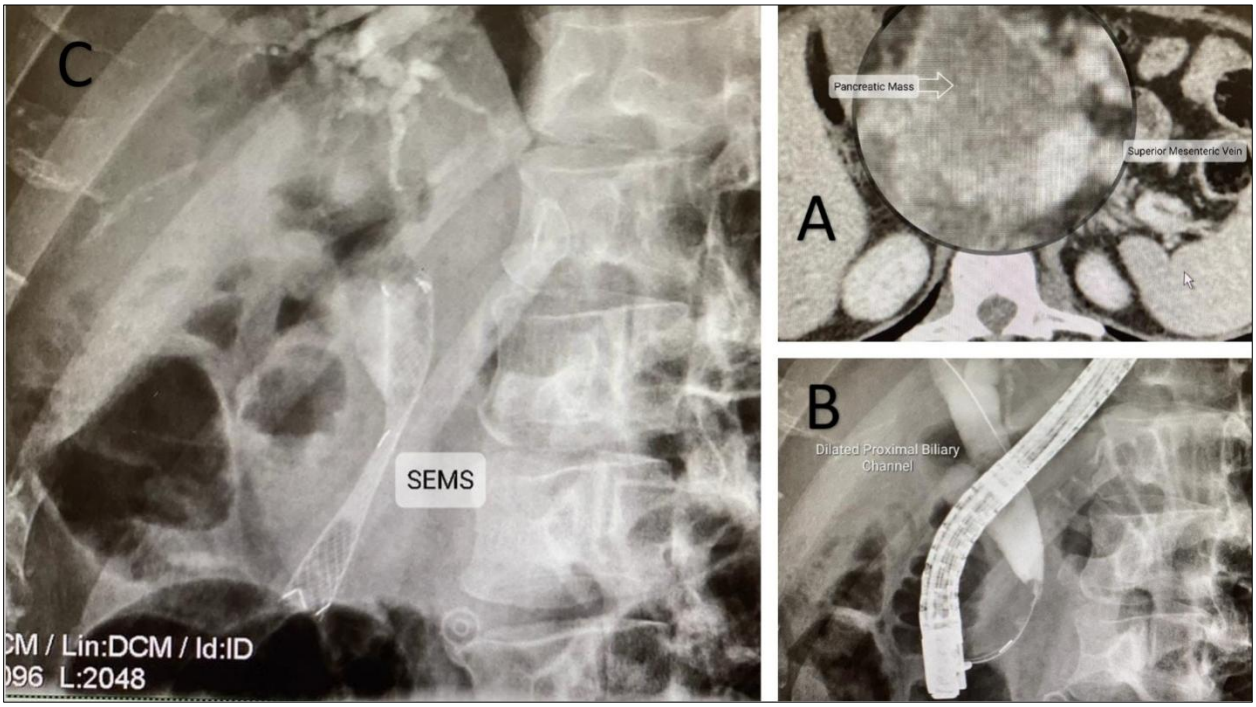

Figure-1

DISCUSSION

Due to the small number of instances that have been recorded globally, there is a lack of clinical data and information available regarding PHSF. The disease is described as severe hepatocellular cholestasis, induced by drugs, toxins or infection.[1,2] Van Dijk et al. first reported it in 2014 and described it as initial serum bilirubin >255 μmol/L, with persistence of or increasing serum bilirubin levels after 1 week of removal of the underlying trigger, exclusion of obstructive cholestasis by imaging techniques, and no evidence of chronic liver disease prior to the initiating event (i.e. drug or toxin exposure or transient biliary obstruction by stones or tumour).[1] Previous investigations have described a variety of factors, including the use of anabolic steroids, antibiotics and total parenteral feeding, as reasons of persistent hepatocellular secretory failure.

In this case study, we describe a patient who underwent biliary stenting but continued to have persistently elevated bilirubin levels for more than a week as depicted by serum level assays due to biliary blockage brought on by underlying pancreatic cancer. Although there were no further concomitant conditions in this patient that would have pointed to an underlying cause of persistently elevated bilirubin, the persistence of vomiting and rising bilirubin levels following stenting led to the diagnosis of PHSF.

Multiple regimens have been tested for the management of cholestasis. Rifampin, a PXR ligand, successfully reduces cholestasis, pruritus and elevated liver enzyme levels.[4–6] Similarly, Phenobarbital, a Constitutive Androstane Receptor (CAR) agonist, has been used to manage patients with cholestasis, resulting in alleviation of pruritus and decreased serum bile concentrations.[7,8] Rifampicin may be an effective treatment for PHSF patients because it induces the PXR-dependent enzymes CYP3A4, UGT1A1, MRP2, and OsfT.[1] The up regulation of these detoxification enzymes and enhanced coordination with the transport of phase 1 and phase 2 detoxification products are well-identified downstream effects by the constitutive androgen receptor (CAR) and PXR, which play a key role in pharmacological therapy for cholestasis.[1,3] This effect of Rifampicin was also highlighted by Ellis et

al., whereby their study found that rifampicin use increased the mRNA levels of CYP3A4 and UGT1A1 in vitro.[10] In addition, it has been suggested that PHSF may manifest in people who have transporter gene mutation carriers. Seven out of ten patients with PHSF who were enrolled in a study by Mingxia et al. had a UGT1A1 deficiency.[2] Two patients with clinical profiles that approximated those of PHSF were reported by Kadir et al. in another investigation.[9] These patients received consecutive treatments with ursodeoxycholic acid, phototherapy, prednisone, and then rifampin. After using Rifampicin for 5 weeks, blood total bilirubin levels in both cases were reported to have decreased by more than 90%. However, prolonged use of Rifampicin is associated with increased incidence of adverse effects such as GI distress, rash, pancreatitis and deranged LFTs.

Persistent hepatocellular secretory failure remains a challenging condition to diagnose and treat effectively due to limited literature. Further studies should be conducted to establish evidence-based guidelines for timely diagnosis and efficient treatment.

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