

Case Report

ACE-ARBS-induced cholestasis: a case report

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ABSTRACT

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are commonly utilized antihypertensive medications with a proven safety record. Nevertheless, they have been associated with few instances of drug-induced liver injury (DILI), namely cholestatic liver injury. This report details a case of recurrent cholestatic hepatotoxicity linked to both an ACE inhibitor and an angiotensin receptor blocker, emphasizing the diagnostic difficulties and potential for cross-reactivity. A 50-year-old female with hypertension developed progressive jaundice and pruritus two weeks after initiating an ACE inhibitor. Laboratory tests revealed a cholestatic pattern of liver injury, and extensive workup ruled out alternative etiologies. A liver biopsy confirmed drug-induced cholestasis. Following ACEI discontinuation, her liver function improved; however, two months later, she experienced recurrent cholestatic liver injury after switching to an ARB. The ARB was discontinued, and medical management with ursodeoxycholic acid, prednisolone, and N-acetylcysteine was initiated. The patient showed gradual biochemical improvement over follow-up, though prolonged cholestasis was noted. The recurrence of liver injury with the ARB suggests potential cross-reactivity between ACEIs and ARBs in susceptible individuals. ACEI- and ARB-induced cholestasis is a rare but significant adverse effect requiring early recognition and drug discontinuation. This case underscores the importance of considering drug-induced hepatotoxicity in patients with unexplained liver dysfunction and highlights the risk of recurrent injury with ARB substitution.

Keywords: Drug-induced liver injury, Cholestasis, ACE inhibitors, ARBs, Hepatotoxicity, Hypertension

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have a relatively high efficacy and safety profile.^{1,2} However, despite their broad usage and general tolerability, these drugs have been linked with drug-induced liver injury (DILI), and according to Thu et al., increasing the risk by 2.68.³ Among the hepatic complications, cholestatic liver injury is an exceptionally rare manifestation whose sporadic reports are linked to certain ARBs and ACEIs like captopril, ramipril, and lisinopril.⁴ Despite idiosyncratic reactions and immune-mediated processes having been

suggested, the underlying mechanisms of ACEI/ARB-induced cholestasis remain poorly understood.⁵

The range of symptoms with which drug-induced cholestasis presents varies widely; from asymptomatic biochemical abnormalities to jaundice, pruritus, and severe liver dysfunction.⁴⁻⁶ Early recognition and prompt discontinuation of the offending agent are critical to prevent progression and improve outcomes. The rarity of these events therefore provides valuable data on the clinical presentation, diagnostic challenges, and management strategies for such adverse reactions. This report presents a rare case of cholestatic liver injury in a 50-year-old female that is directly linked to the use of an

ACE inhibitor. Her unexpected presentation with progressive jaundice and severe pruritus shows the need for clinicians to consider drug-induced hepatotoxicity in patients with unexplained liver dysfunction. Furthermore, the case demonstrates the potential for recurrent hepatotoxicity with candesartan, which further complicates treatment. This case not only emphasizes the importance of early identification and management of DILI but also highlights the diagnostic challenges posed by rare adverse drug reactions in routine clinical practice.

CASE REPORT

A 50-year-old female with a history of hypertension was prescribed an ACE inhibitor for blood pressure management. The patient developed progressive jaundice, generalized pruritus, dark urine, and pale stools, just two weeks into therapy, which prompted her to seek medical attention. She had no history of alcohol use, viral hepatitis, or exposure to other hepatotoxic agents. The patient reported significant fatigue and itching that interfered with her daily activities. There was no associated abdominal pain, fever, or gastrointestinal symptoms such as nausea or vomiting. Physical examination revealed icteric sclerae and jaundiced skin but was unremarkable. There was no hepatomegaly, splenomegaly, or ascites, and her abdomen was soft and non-tender. Peripheral stigmata of chronic liver disease were notably absent while cardiovascular and respiratory examinations were normal.

Upon further examination, laboratory investigations showed markedly elevated liver enzymes with a cholestatic pattern: Aspartate aminotransferase (AST): 140 U/L, Alanine aminotransferase (ALT): 160 U/L, Alkaline phosphatase (ALP): 1565 U/L, Total bilirubin: 44 $\mu\text{mol/L}$, Direct bilirubin: 33 $\mu\text{mol/L}$, Albumin: 32 g/L, and INR: 1 IU. Her prothrombin time (PT) and international normalized ratio (INR) were within the normal limits.

Viral serologies for hepatitis A, B, C, and E, and tests for Epstein-Barr virus and cytomegalovirus, were all negative. Antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and liver-kidney microsomal antibodies, were also negative. Serum immunoglobulin levels and tests for metabolic liver diseases were within normal limits. An abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) revealed gallbladder stones with no evidence of cholecystitis, normal common bile duct (CBD) caliber at 4 mm, and no evidence of stones within the visualized part of the CBD. The liver was normal in size and echotexture, with no signs of fatty infiltration.

Given the lack of an identifiable cause, a liver biopsy was performed to establish a definitive diagnosis. Histopathological examination showed chronic hepatitis with dense portal lymphoplasmacytic infiltrate (Figure 1), marked intrahepatic cholestasis, and mild lobular necro inflammatory activity (Figure 2). No fibrosis or copper deposition was noted, and the findings were consistent

with drug-induced liver injury. The absence of eosinophilia and granulomas suggested a non-allergic, idiosyncratic reaction (Figure 3).

A detailed review of her medication history confirmed that the ACE inhibitor was the only new medication introduced in the past year. As a consequence, the ACE inhibitor was promptly discontinued after which the patient followed up one month later, showing a marked regression of liver enzymes: AST 99 U/L, ALT 74 U/L, ALP 760 U/L, total bilirubin 26 $\mu\text{mol/L}$, and direct bilirubin 20 $\mu\text{mol/L}$. However, two months later, she presented again with severe jaundice, pruritus, and fatigue after being switched to candesartan. Laboratory investigations revealed worsening liver function with AST 83 U/L, ALT 47 U/L, ALP 1265 U/L, total bilirubin 140 $\mu\text{mol/L}$ (direct bilirubin 110 $\mu\text{mol/L}$), albumin 26 g/L, and INR 1 IU. Medication discontinuation and initiation of ursodeoxycholic acid, prednisolone, and N-acetyl cysteine led to prolonged cholestasis with partial biochemical improvement.

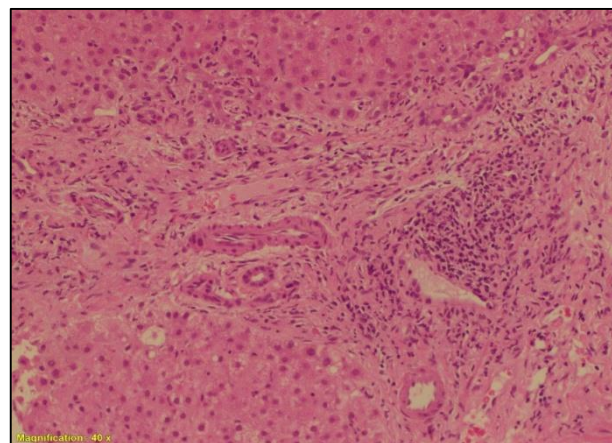


Figure 1: Histopathological examination at 40X magnification showing canaliculal cholestasis and mild hepatocellular injury.

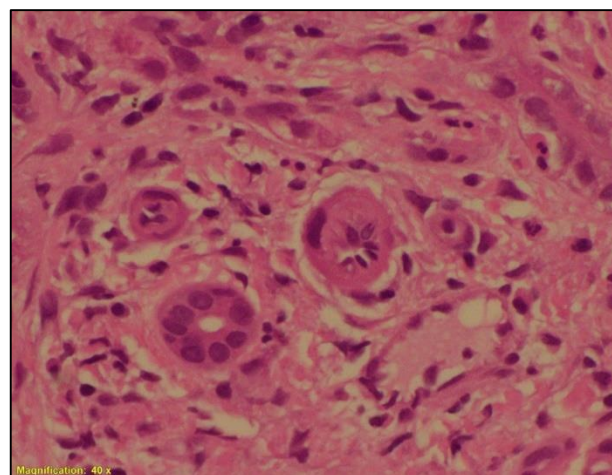


Figure 2: High magnification (40X) highlighting portal inflammation with minimal inflammatory cell infiltration.

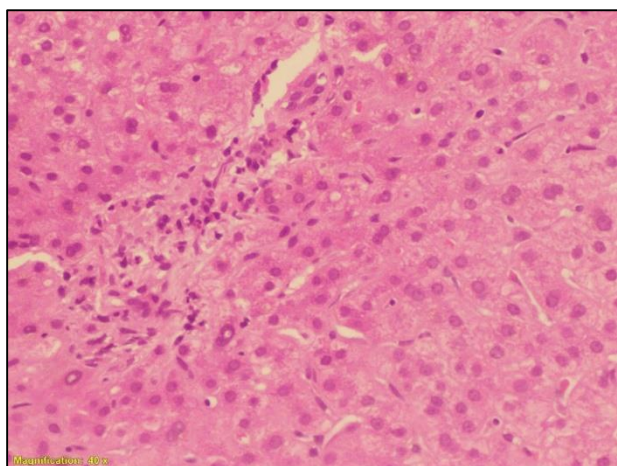


Figure 3: Liver biopsy demonstrating hepatocellular changes with no evidence of fibrosis or copper deposition.

DISCUSSION

ACE inhibitors and ARBs are seldom implicated in hepatotoxicity, and cholestatic injury is an even rarer occurrence. A limited number of cases have been documented in the literature, with most involving cholestatic or mixed patterns of liver injury. Forner et al, reported a case of ramipril-associated cholestasis in a 67-year-old male with a history of methimazole-induced liver injury two decades earlier.⁴ The patient developed prolonged cholestasis despite discontinuation of the drug, requiring a six-week hospital stay and prolonged follow-up. Unlike rapid clinical improvement following drug cessation demonstrated in our case, Forner's case highlights the possibility of recurrent DILI with cross-reactivity between medications.

Al-Rifaie et al, reported a fatal case of lisinopril-induced cholestatic liver injury involving a 54-year-old male and the challenges of managing severe outcomes when diagnosis is delayed.⁷ Their case demonstrated a more aggressive clinical course compared to our report. Unlike our patient who sought medical attention early, the delayed recognition in their case led to severe liver dysfunction, coagulopathy, and eventual liver failure requiring transplant consideration.

Douros et al, presented a case of ramipril-induced liver injury confirmed by a positive rechallenge whose findings underscored the hepatotoxic potential of ramipril which was evidenced by a dramatic rise in ALT levels upon re-exposure and a rapid decline following discontinuation.⁸ Alongside the 65 reports retrieved from the FAERS database, Douros et al, highlighted jaundice as the most frequent hepatic adverse event associated with ramipril.⁸ These insights align with our case by demonstrating the varied presentations and outcomes of ACEI-induced hepatotoxicity and the importance of early drug withdrawal.

Singh et al published a case study in 2014 that documented the first instance of lisinopril-induced hepatotoxicity presenting through a cholestatic mechanism, contrasting with previous reports that primarily described a hepatocellular pattern of injury.⁹ The patient developed symptoms two years after initiating lisinopril. The long duration before symptoms started to show is an important factor to consider in the potential for a delayed onset of liver injury.⁹ Unlike Singh et al case, where symptoms took two years to manifest, our patient exhibited a rapid onset of liver dysfunction; the recurrent cholestasis observed following the switch from Ramipril to Candesartan is testament to the challenge of cross-reactivity among ACE inhibitors and ARBs.

CONCLUSION

The exact pathophysiology of ACEI/ARB-induced cholestasis remains elusive. The absence of eosinophilia and systemic hypersensitivity features in this case strongly suggests a non-immune mechanism with metabolic disruption potential. The recurrence of symptoms with candesartan highlights the risk of cross-reactivity and the need for close follow-up. However, cases with delayed diagnosis or continued exposure to the offending drug have shown prolonged recovery or even fatal outcomes. Clinicians must maintain a high index of suspicion for DILI in patients presenting with unexplained liver dysfunction especially upon the introduction of new medications.

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