A Case of Drug-Induced Liver Injury with Cholestasis Following Lamotrigine Therapy: Successful Management via Biliary Reconstruction

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Abstract

This report describes a 29-year-old male with neocortical epilepsy who developed severe mucocutaneous adverse reactions and subsequent acute drug-induced liver injury during treatment with lamotrigine. Despite prompt drug discontinuation and standard liver-protective therapy, the patient progressed to severe cholestatic liver disease, culminating in secondary biliary cirrhosis. Due to the failure of medical management, the patient underwent surgical biliary reconstruction (Roux-en-Y hepaticojejunostomy), which led to gradual recovery of liver function and significant improvement in overall condition. This case highlights the potential for severe hepatotoxicity associated with lamotrigine and illustrates the role of surgical intervention as a salvage therapy for patients with end-stage drug-induced cholestatic liver disease.

Keywords: Lamotrigine, drug-induced liver injury, cholestasis, biliary reconstruction surgery, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), refractory epilepsy

1. Introduction

Lamotrigine is widely used in the management of epilepsy and bipolar disorder [1]. Among its most

significant adverse effects are cutaneous reactions, which range from mild maculopapular eruptions to life-threatening conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [2]. In addition to dermatologic manifestations, lamotrigine has been associated with drug-induced liver injury (DILI), though this typically presents as transient elevation of liver enzymes [3]. Progression to acute liver failure or severe cholestatic cirrhosis necessitating surgical intervention remains exceedingly rare. Here, we report a case of severe, progressive lamotrigine-induced liver injury that ultimately required biliary reconstruction surgery.

2. Case Presentation

A 29-year-old male was admitted to the Department of Neurosurgery at Lanzhou University Second Hospital with a chief complaint of recurrent limb convulsions over 17 years, exacerbated in the past six months. During hospitalization, his therapeutic regimen was adjusted based on clinical symptoms, electroencephalogram findings (Figure 1), and neuroimaging results (Figure 2). Following this adjustment, the patient developed skin rash, jaundice, and abnormal liver function.

The patient had a long-standing history of drug-resistant epilepsy previously managed with multiple antiepileptic drugs including valproate and levetiracetam, all with suboptimal efficacy. Upon multidisciplinary team (MDT) recommendation, lamotrigine was introduced following a standardized dose-escalation protocol. Approximately two weeks after reaching the target maintenance dose, the patient presented with generalized erythematous maculopapular rash and fever (peak temperature 38.5°C). A preliminary diagnosis of drug eruption was made, leading to immediate discontinuation of lamotrigine and initiation of glucocorticoid and antihistamine therapy. The left mesial temporal lobe and periventricular areas are also indicated on the metabolic map. Although the rash partially resolved, the patient subsequently developed scleral and cutaneous jaundice, tea-colored urine, and clay-colored stools. Laboratory investigations (2 weeks after drug cessation) revealed: total bilirubin (TBil) 392 μmol/L, direct bilirubin (DBil) 312.1 μmol/L, indirect bilirubin (IBil) 79.9 μmol/L, alanine aminotransferase (ALT) 366 U/L, aspartate aminotransferase (AST) 722 U/L, alkaline phosphatase (ALP) 683 U/L, and gamma-glutamyl transferase (GGT) 807 U/L.

Serological testing showed negative markers for hepatitis A, B, C, and E viruses, and negative

autoantibody panels for autoimmune liver diseases. Imaging studies: abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) demonstrated preserved liver size and morphology with mildly increased parenchymal echogenicity/heterogeneity. Intrahepatic bile ducts were visualized without dilation or filling defects. The pancreas appeared enlarged with multiple patchy abnormal signals in the body and tail, suggestive of inflammatory changes. Esophagogastroduodenoscopy revealed chronic atrophic gastritis with erosion and duodenitis. Diagnosis: Lamotrigine-induced drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DiHS) accompanied by severe cholestatic drug-induced liver injury, secondary biliary cirrhosis (decompensated), and neocortical epilepsy. Clinical course: The patient received comprehensive medical management including ursodeoxycholic acid, S-adenosylmethionine, and tapered glucocorticoids. However, after two weeks of treatment, the patient exhibited progressive jaundice, refractory pruritus, and weight loss (Figure 3), with no improvement in liver biochemical parameters, indicating failure of medical therapy and suggesting irreversible biliary obstruction.

Following a multidisciplinary team (MDT) consultation involving hepatology, hepatobiliary surgery, gastroenterology, and neurology, the patient was diagnosed with end-stage cholestatic liver disease, with structural damage to the biliary system identified as the primary pathology. Surgical biliary reconstruction was recommended to relieve cholestasis. The patient and family subsequently sought treatment at West China Hospital. Under general anesthesia, exploratory laparotomy revealed a dark green, firm liver with nodular surface changes. The common bile duct and hilar bile ducts exhibited severe fibrosis and stenosis. Consequently, the patient underwent cholecystectomy, resection of the common bile duct, and Roux-en-Y hepaticojejunostomy. The procedure was completed successfully. The patient recovered well postoperatively, with gradual resolution of jaundice and marked alleviation of pruritus. At one-month follow-up, total bilirubin had decreased to 85 μmol/L, ALT and AST normalized, and ALP and GGT levels showed significant improvement. Three months after surgery, the patient remained in stable condition with restored mental and appetite status, continued amelioration of liver function, and well-controlled seizures under an adjusted antiepileptic regimen utilizing non-hepatotoxic agents.

3. Discussion

Severe lamotrigine-induced liver injury represents one of its most dangerous complications, likely mediated by an idiosyncratic immune reaction [4]. The present case exhibited a classic clinical progression of DiHS/DRESS, characterized by fever, rash, and hepatic involvement. Its distinctive feature was the manifestation of exceptionally refractory and severe cholestasis, which ultimately progressed to cirrhosis necessitating surgical intervention. In cases of drug-induced liver injury, the primary measures include immediate discontinuation of the offending agent and initiation of medical supportive therapy. However, when the biliary system sustains severe damage, creating an "anatomic" obstruction to intrahepatic bile flow, medical management often proves inadequate. In such scenarios, biliary reconstruction surgery, by establishing alternative drainage pathways, becomes the only effective means to salvage liver function and improve quality of life. Roux-en-Y hepaticojejunostomy is a well-established procedure for benign biliary strictures and obstruction [5], which in this case successfully restored bile drainage and reversed the trajectory of hepatic functional decline.

4. Literature Review

4.1. Epidemiology and Mechanisms of Lamotrigine-Associated Drug-Induced Liver Injury

Lamotrigine, a broad-spectrum antiepileptic drug, is an uncommon but one of the most serious causes of drug-induced liver injury (DILI). Literature reports indicate that while lamotrigine-associated DILI accounts for less than 7.6% of all DILI cases, the proportion progressing to acute liver failure can be as high as 1.9% among these affected individuals [6]. The hepatotoxicity is primarily attributed to an idiosyncratic reaction, linked to host metabolic and immune factors. Lamotrigine is predominantly metabolized in the liver via glucuronidation. In susceptible individuals, this process may generate reactive intermediates that deplete hepatic glutathione, leading to oxidative stress and hepatocellular damage. Furthermore, lamotrigine is a well-established causative agent of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Drug-Induced Hypersensitivity Syndrome (DiHS) [6]. This syndrome is characterized by rash, fever, lymphadenopathy, and multi-organ involvement, with the liver being a frequently affected site [6]. The underlying mechanism involves an exaggerated T-cell-mediated immune response, often associated with specific human leukocyte antigen (HLA) alleles, resulting in massive cytokine release and subsequent organ damage [7]. The sequence of symptoms in our patient—initial rash and fever followed by severe liver injury—closely aligns with the typical clinical presentation of DRESS syndrome.

4.2. From Acute Liver Injury to Cholestatic Cirrhosis: Pathophysiology and Clinical Trajectory

Lamotrigine-induced liver injury can manifest in hepatocellular, cholestatic, or mixed patterns [8]. Among these, cases presenting with severe cholestasis are relatively uncommon but carry a poorer prognosis. Bile duct injury is a central pathogenic mechanism. In DRESS syndrome, activated T-cells target biliary epithelial cells [9], potentially leading to vanishing bile duct syndrome (VBDS). The progressive destruction and loss of interlobular bile ducts disrupt normal bile excretion, resulting in profound and refractory intrahepatic cholestasis. Persistent cholestasis activates hepatic stellate cells, promoting collagen deposition and hepatic fibrosis. If the bile duct injury becomes irreversible, fibrosis progresses relentlessly, culminating in secondary biliary cirrhosis within months. This contrasts sharply with viral or alcoholic cirrhosis, which typically evolves over decades. The rapid clinical course in our patient—progressing from acute liver injury to surgically addressed cirrhosis within months—exemplifies this accelerated trajectory.

4.3. The Role of Biliary Reconstruction in Drug-Induced Cholestatic Cirrhosis

Therapeutic options for end-stage cholestatic liver disease refractory to medical management remain severely limited. While ursodeoxycholic acid and glucocorticoids represent first-line therapies for cholestasis, they provide only palliative benefit once severe architectural destruction of the bile ducts has occurred, as they cannot address the fundamental mechanical obstruction to bile flow. For decompensated cirrhosis and liver failure, liver transplantation remains the established standard of care [10]. However, biliary reconstruction surgery—such as Roux-en-Y hepaticojejunostomy—may serve as an alternative or bridging intervention in selected cases where the primary obstruction is localized to the extrahepatic or hilar large ducts, and sufficient functional hepatic reserve is preserved. The rationale is to bypass the fibrotic and stenotic extrahepatic biliary system, establishing an alternative conduit for biliary drainage, thereby "unloading" the liver and potentially delaying or avoiding the need for transplantation [11].

Notably, reports of biliary reconstruction for diffuse drug-induced intrahepatic biliary strictures are exceedingly scarce in the literature, with most surgical series focusing on biliary strictures secondary to primary sclerosing cholangitis or iatrogenic injury. The successful outcome in our case suggests that for carefully selected patients with drug-induced cirrhosis predominantly driven by large duct obstruction,

biliary reconstruction may represent a viable salvage procedure. This approach offers a potential therapeutic avenue for patients ineligible for immediate transplantation or those seeking to postpone it.

In summary, the singular importance of this case lies in its comprehensive and severe disease trajectory, which delineates a complete clinical spectrum from lamotrigine-induced DRESS syndrome to severe vanishing bile duct syndrome (VBDS), culminating in rapidly progressive biliary cirrhosis necessitating surgical intervention. Therapeutically, this case demonstrates a paradigm shift by successfully exploring biliary reconstruction as a viable "intermediate pathway" between conventional medical therapy and liver transplantation. This experience provides invaluable clinical insights for managing similar rare and critical cases. Furthermore, this case exemplifies the critical role of multidisciplinary team (MDT) collaboration, involving neurology, hepatology, and hepatobiliary surgery, in the successful management of complex drug-induced injuries. The integrated approach was decisive in navigating the diagnostic and therapeutic challenges presented by this severe adverse drug reaction.

5. Conclusion

This case provides a critical demonstration of the potential for lamotrigine-induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) to rapidly progress to severe cholestatic liver disease characterized by vanishing bile duct syndrome (VBDS), ultimately resulting in secondary biliary cirrhosis. This aggressive clinical course offers crucial insights: vigilance and early recognition are paramount. Clinicians initiating lamotrigine, particularly during dose titration, must maintain a high index of suspicion for its severe dermatologic and hepatotoxic potential. The appearance of prodromal signs of hypersensitivity, such as rash or fever, warrants immediate, permanent drug discontinuation and comprehensive monitoring, representing the most critical step in halting disease progression.

Multidisciplinary collaboration and proactive surgical intervention can be lifesaving. Once a patient develops refractory cholestasis unresponsive to medical therapy, early evaluation by a multidisciplinary team is essential. This case confirms that for carefully selected patients in whom large-duct obstruction is the dominant pathology, biliary reconstruction serves as a viable salvage therapy. It can effectively restore biliary drainage, reverse hepatic functional decline, and potentially obviate the need for liver transplantation.

In summary, although lamotrigine-induced end-stage liver disease requiring surgical intervention is exceedingly rare, its life-threatening nature mandates that this risk be acknowledged as one of its most severe long-term complications. While this report offers a novel management paradigm for such critical cases, the long-term efficacy of biliary reconstruction and its ideal candidate profile require further validation through additional case accumulation and extended follow-up.

Authorship contribution statement

Xiaoqiang Wang: writing - review & editing, writing - original draft, conceptualization. Ying Dang: Writing - review & editing, supervision, resources, conceptualization.

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Competing Interests

None.

Funding

None.

Consent

None.

Ethical Statement

This study was approved by the Ethics Committee of Lanzhou University Second Hospital and written informed consent was obtained from the patient and his family.

Data Availability

No datasets were generated or analysed during the current study.

Fig. 1. Medical image post-processing.

Multiple scattered micro-ischemic foci in the bilateral subcortical regions. Hypometabolism is observed in the left hippocampus compared to the right, as well as in the left parietal lobe (angular gyrus).

Fig. 2. Electroencephalography findings.

Interictal Epileptiform Discharges: During wakefulness and sleep states, a moderate amount of low- to high-amplitude spike/sharp and wave complexes, occurring sporadically, were observed over the left mid- to posterior temporal region. During sleep, a small number of low- to high-amplitude spike/sharp waves, occurring sporadically, were recorded from the right inferior temporal region. Background Activity: The posterior dominant rhythm was slightly slower than expected for the patient's age group.

Fig. 3. Clinical manifestations of lamotrigine hypersensitivity.

A) Scleral icterus presenting following lamotrigine-induced drug hypersensitivity. **B)** Maculopapular rash distributed across the upper back attributable to lamotrigine hypersensitivity. **C)** Maculopapular eruptions observed bilaterally on the lower extremities, consistent with lamotrigine adverse drug reaction.

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