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Propafenone-Induced Cholestatic Liver Injury: When Diagnosis Does Not Skip a Beat

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Keywords
Drug-induced liver injury · Cholestatic liver injury · Propafenone

Abstract
Introduction: Propafenone is a widely used class Ic antiarrhythmic drug that is mainly metabolised by the liver. Hepatotoxicity associated with propafenone is rare, with only a few clinical cases reported in the literature. ***Case Presentation:*** We presented a case of propafenone-related hepatotoxicity, with cholestatic liver injury and development of jaundice and pruritus within 3 to 4 weeks of treatment initiation. Three months after discontinuation, the patient was asymptomatic, and all liver tests normalised. ***Conclusion:*** With this clinical case, we aimed to emphasise the importance of the medication history and the exclusion of other possible causes of altered liver enzymes.

Lesão hepática colestática induzida pela propafenona: quando o diagnóstico não perde o ritmo

Palavras Chave
Disfunção hepática induzida por fármacos · Lesão hepática colestática · Propafenona

Resumo
Introdução: A propafenona é um fármaco anti-arrítmico de classe Ic amplamente utilizado que é maioritariamente metabolizado pelo fígado. A hepatotoxicidade associada à propafenona é rara, com poucos casos clínicos publicados na literatura. ***Apresentação do caso:*** Apresentamos um caso de hepatotoxicidade associada à propafenona com lesão hepática colestática e desenvolvimento de prurido e icterícia dentro de três a quatro semanas após o início da terapêutica. Três meses após suspender a propafenona, a doente estava assintomática e com os parâmetros analíticos hepáticos normalizados. ***Conclusão:*** Com este caso clínico, pretendemos realçar a

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importância da colheita da história medicamentosa e a exclusão das restantes causas possíveis de alteração das enzimas hepáticas.

Introduction

Propafenone is a class Ic antiarrhythmic agent that blocks open sodium channels and outward potassium channels, leading to a decrease in cardiac automaticity, an increase in refractory periods and slowed cardiac conduction [1, 2]. It is mainly metabolised by the liver [2]. Hepatotoxicity associated with propafenone is rare, with less than ten other clinical cases reported [3]. In this article, we aimed to describe a new case of hepatotoxicity related to propafenone, emphasising the importance of the medication history and thorough exclusion of other possible causes of altered liver enzymes.

Case Presentation

A 64-year-old female patient presented to the emergency department in August of 2023 with fever, generalised abdominal pain, diarrhoea with 8–10 liquid stools per day, without mucus or blood, and unintentional weight loss of 4 kg (6.7% of total body weight) in the previous 10 days. On observation, the patient was febrile with a temperature of 38.5°C, and the abdominal examination was unremarkable. Analytically, the patient had acute kidney injury (AKI) with a creatinine of 1.47 mg/dL (AKI stage 2) without ionic changes. The patient had alterations in liver parameters with aspartate aminotransferase 107 IU/L (upper limit of normal [ULN] 40 IU/L), alanine aminotransferase (ALT) 193 IU/L (ULN 40 IU/L), gamma-glutamyl transferase 346 IU/L (ULN 73 IU/L), and alkaline phosphatase (ALP) 707 IU/L (ULN 116 IU/L), without hyperbilirubinemia (R ratio 0.8). Abdominal ultrasound showed a normal liver parenchyma and no other changes, namely, dilatation of the intra- and extrahepatic bile ducts, choledocholithiasis, or gallstones. The patient denied alcohol consumption or illicit drug abuse.

Medical history was significant for arterial hypertension and dyslipidaemia, with long-term treatment with lercanidipine, azilsartan medoxomil, atorvastatin, and bisoprolol. In addition, a recent episode of atrial fibrillation with rapid ventricular response was reported, for which amiodarone and rivaroxaban were initiated. Two weeks prior to admission, the patient developed amiodarone-induced hypothyroidism, requiring the initiation of levothyroxine 0.05 mg and the replacement of amiodarone with propafenone 150 mg twice daily. The timeline of the medication changes is shown in Figure 1.

The patient was admitted to the hospital with suspension of lercanidipine, azilsartan medoxomil, atorvastatin and rivaroxaban, but, after cardiology consultation, levothyroxine, bisoprolol, and propafenone were continued and subcutaneous enoxaparin was started. Stool culture was positive for *Citrobacter freundii*. Parasitological analysis was unremarkable, including negative for *Entamoeba histolytica*. The patient was treated with meropenem 1 g every 8 h with resolution of fever and diarrhoea, AKI was corrected with fluid therapy. Regarding the alterations in liver parameters, viral serological markers were negative, including for hepatitis B virus, human immunodeficiency virus, and hepatitis C virus, as well as IgM for Epstein-Barr virus, varicella-zoster virus, cytomegalovirus, and herpes simplex virus (with positive IgG) and positive IgG antibodies for hepatitis A virus. Hepatitis E virus serology was negative for IgM and positive for IgG, with negative tests for Hepatitis E virus RNA. Serologies for *Brucella*, *Rickettsia conorii*, *Leptospirosis*, *Leishmania*, and *Fasciola* were negative, as was the Widal reaction. Anti-nuclear, anti-smooth muscle, anti-mitochondrial and anti-liver/kidney microsomal antibodies' levels were within normal limits, as were immunoglobins, iron kinetics, alpha-1 antitrypsin, and ceruloplasmin. Antibodies to celiac disease were also negative. The serological and metabolic tests performed are summarised in Table 1.

During hospitalisation, despite the control of gastrointestinal symptoms, there was a worsening of the cholestatic liver dysfunction, with the development of conjugated hyperbilirubinemia (maximum values of total bilirubin 5.23 mg/dL and direct bilirubin 3.8 mg/dL). Additionally, thyroid function tests remained stable during hospitalisation, and the dose of levothyroxine was continued at 0.05 mg. Therefore, the patient underwent endoscopic ultrasound, which showed a common bile duct with a slightly thickened wall, maintaining normal calibre throughout its entire length and without endoluminal content. No other changes were identified in the gallbladder, pancreas, Wirsung's canal, and Vater's papilla. She had a permeable portal and splenic veins and permeable mesenteric vessels of normal calibre, and the left hepatic lobe showed no alterations. Since there were no abnormalities to justify the cholestatic liver dysfunction, with conjugated hyperbilirubinemia, a liver biopsy was performed in the same procedure, guided by

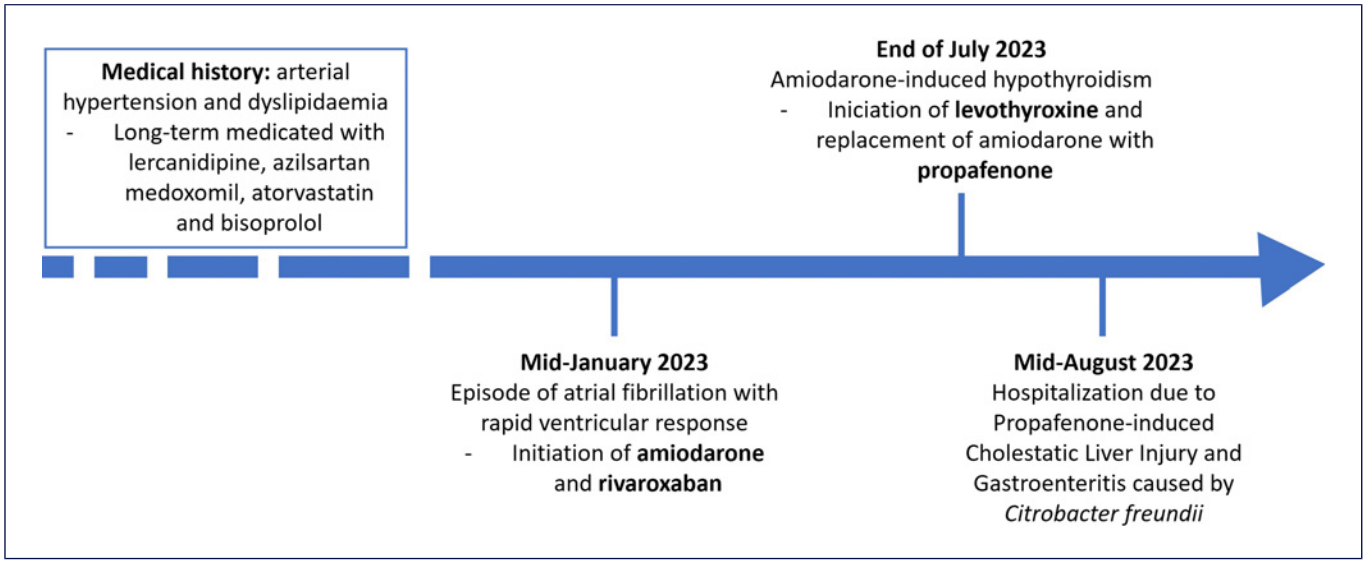

Fig. 1. Illustrated timeline of medication changes.

endoscopic ultrasound, with 4 needle passages, using a 22-gauge FNB needle, from MICRO-TECH (Nanjing) Co., Ltd. Histological examination showed a fragmented sample, with 2.5 cm and a total of 8 portal tracts, and non-specific alterations, with portal tracts enlargement with infiltrates of lymphocytes and macrophages and macrovesicular steatosis. Images of the endoscopic ultrasound are shown in Figure 2, and images of the liver biopsy are shown in Figure 3.

In view of the persistence of cholestatic liver dysfunction and conjugated hyperbilirubinemia, the non-specific findings on liver biopsy, and although there are only a few cases of hepatotoxicity associated with propafenone, it was decided to discontinue propafenone after discussion with the cardiology department regarding the risks and benefits of maintaining the antiarrhythmic drug. Withdrawal of propafenone was associated with a gradual but immediate decrease in aminotransferase levels, bilirubin, gamma-glutamyl transferase, and ALP. The evolution of clinical and analytical parameters during hospitalisation is shown in Figure 4. Three months after propafenone suspension, normalisation of all liver tests was observed.

Discussion

The Roussel Uclaf Causality Assessment Method (RUCAM) is widely used to assess the causality of drug-induced liver injury (DILI) [4–6]. Recently, the Revised Electronic Causality Assessment Method (RECAM), a semi-automated, computerised causality assessment tool using standardised, quantitative, and categorical data fields, has been developed and is currently available as an online calculator [7, 8]. In our patient, a diagnosis of acute propafenone hepatotoxicity was considered probable with a RUCAM score of 8 points, as summarised in Table 2, and highly probable with a RECAM score of 11 points.

Our patient had fever, abdominal pain and diarrhoea and was diagnosed with gastroenteritis caused by *C. freundii*, which added to the complexity of the case. *C. freundii* is usually considered to be a commensal species of the human gut [9]. However, some isolates have acquired specific virulence properties with high rates of multidrug resistance, enabling them to cause diarrhoea [9, 10]. Indeed, *C. freundii* isolates from diarrhoeal patients and healthy individuals have been shown to have different sequence types, antibiotic resistance profiles and virulence properties [11]. *C. freundii* has been associated with hepatobiliary tract infections and liver abscesses [12], and there are a few case reports of *Citrobacter koseri* abscesses, which are mainly an opportunistic or a nosocomial pathogen but can also affect immunocompetent individuals [13–15]. In our case, gastroenteritis caused by *C. freundii* was treated with meropenem due to the exuberance of the clinical picture with fever, diarrhoea with 10 liquid stools per day and unintentional weight loss of almost 10% of the total body weight, with an evolution period of 10 days.

Table 1. Serological and metabolic tests performed

Viral serologies	
Anti-HBs	Negative
HBs antigen	Negative
Anti-HBc	Negative
Anti-HAV IgG	Positive
Anti-HIV	Negative
Anti-HCV	Negative
Anti-HEV IgG	Negative
Anti-HEV IgM	Negative
RNA HEV	Negative
EBV IgG	Positive
EBV IgM	Negative
VZV IgG	Positive
VZV IgM	Negative
CMV IgG	Positive
CMV IgM	Negative
HSV type 1 IgG	Positive
HSV type 1 IgM	Negative
Other serologies	
Brucella	Negative
Rickettsia conorii	Negative
Leptospirosis	Negative
Leishmania	Negative
Fasciola	Negative
Widal's reaction	Negative
Hepatic autoimmunity tests	
Anti-nuclear antibodies	Negative
Anti-smooth muscle antibodies	Negative
Anti-mitochondrial antibodies	Negative
Anti-liver/kidney microsomal antibodies	Negative
Immunoglobins, mg/dL	
IgM	187 (50–350)
IgA	230 (40–350)
IgG	977 (650–1,600)
IgG1	536 (240–1,118)
IgG2	389 (124–549)
IgG3	30 (21–134)
IgG4	44 (7–89)
Iron kinetics	
Serum iron, µg/dL	53 (50–170)
Total iron binding capacity, µg/dL	260 (250–425)
Transferrin saturation, %	20.4
Ferritin, ng/mL	631 (10–291)
Alpha-1 antitrypsin, mg/dL	189 (78–200)
Ceruloplasmin, mg/dL	45 (25–63)
Antibodies to celiac disease	Negative
Lipid profile, mg/dL	
Total cholesterol	123 (<200)
HDL-cholesterol	21 (40–60)
LDL-cholesterol	74 (<130)
Triglycerides	139 (30–150)
Glycated haemoglobin, %	5.9

Table 1 (continued)

Thyroid function tests	
TSH, μIU/mL	2.495 (0.55–4.78)
Free T4, ng/dL	1.17 (0.89–1–76)

Anti-HBs, hepatitis B surface antibody; anti-HBc, hepatitis B core antibody; HAV, hepatitis A virus; HIV, human immunodeficiency virus; HCV, hepatitis C virus; HEV, hepatitis E virus; EBV, Epstein-Barr virus; VZV, varicella-zoster virus; CMV, cytomegalovirus; HSV, herpes simplex virus; HDL-cholesterol, high-density cholesterol; LDL-cholesterol, low-density cholesterol; TSH, thyroid-stimulating hormone; T4, thyroxine.

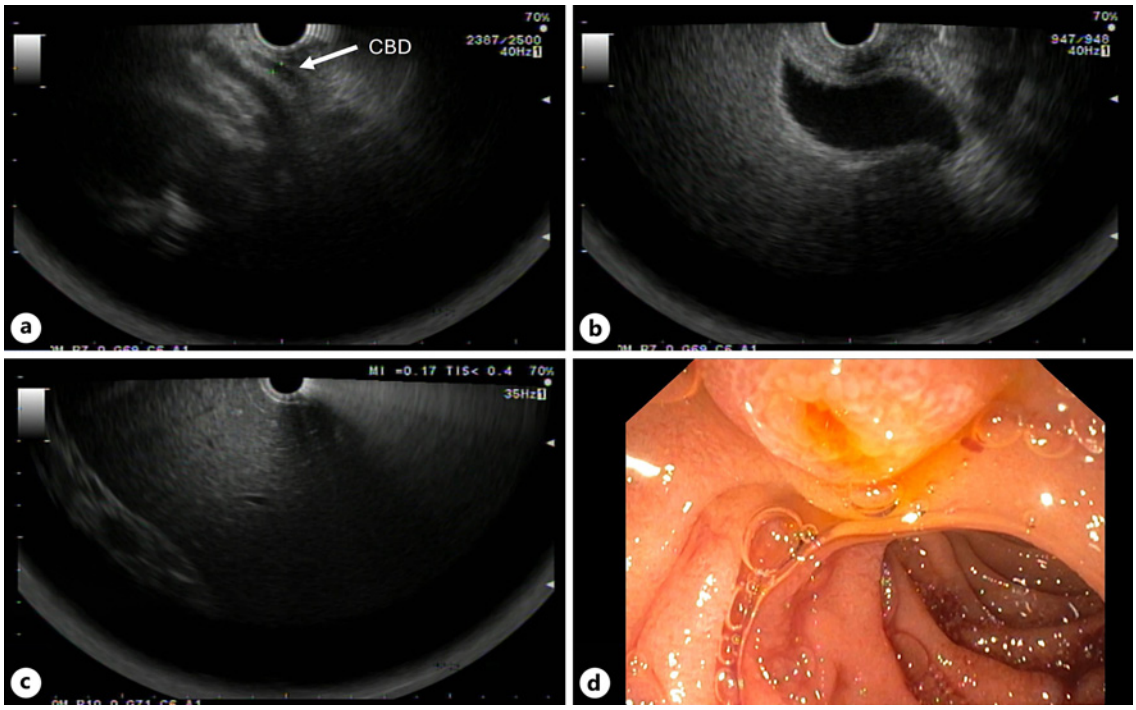

Fig. 2. Images of the endoscopic ultrasound. **a** Common bile duct (CBD). **b** Gallbladder. **c** Left hepatic lobe and endoscopic images. **d** Vater's papilla.

However, cefotaxime, cefepime and piperacillin-tazobactam were effective alternatives, as high percentages of *Citrobacter* species susceptible to these antibiotics have been described in patients with *Citrobacter* bacteraemia [16]. In addition, sepsis and prolonged hypotension associated with the dehydration caused by the gastroenteritis due to *Citrobacter* infection can lead to liver dysfunction and ischaemic hepatitis [17, 18]. However, in ischaemic hepatitis, there is a rapid rise in both aspartate aminotransferase and alanine aminotransferase (>10–50 ULN), followed by rapid improvement, with minimal changes in ALP and bilirubin levels [18]. Other drugs may also be associated with DILI, namely meropenem and levothyroxine. The use of meropenem to treat gastroenteritis due to *Citrobacter* infection may have exacerbated cholestatic liver dysfunction. Indeed, there are case reports of meropenem causing mixed hepatocellular and cholestatic liver injury [19, 20] and even a vanishing bile duct syndrome [21]. In our case, these possibilities were ruled out by the persistent worsening of liver dysfunction after resolution of the gastroenteritis and discontinuation of meropenem. Finally, levothyroxine has been reported as a rare cause of acute liver injury, attributed to a higher initial dose, a more rapid increase in dose, or a hypersensitivity reaction [22–24]. In our patient, the levothyroxine dose was stable from the start of treatment and even during hospitalisation.

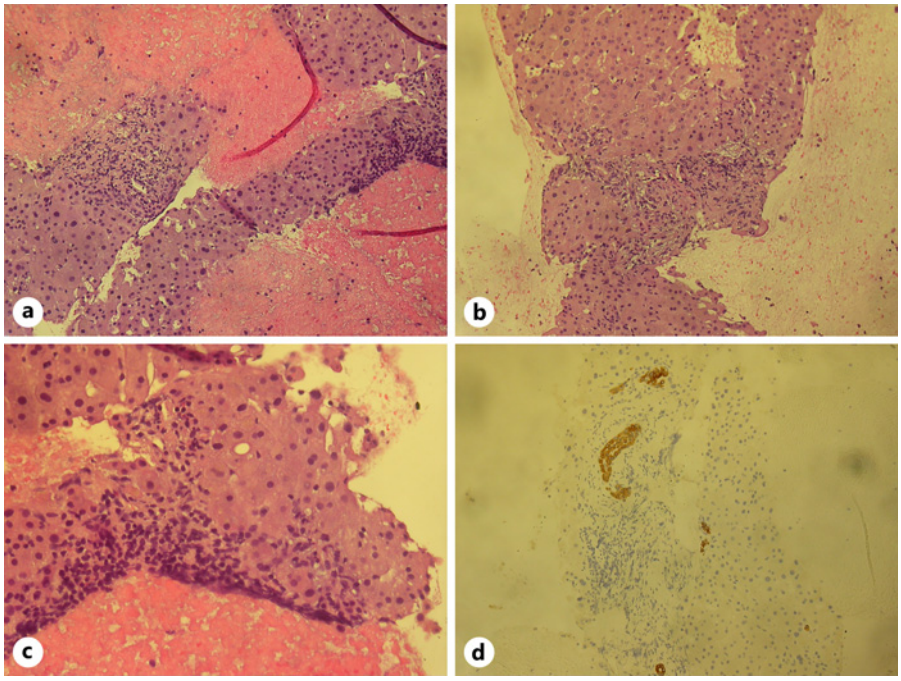

Fig. 3. Histologic images of the liver biopsy. Inflammation and lymphocytic infiltration in haematin-eosin colouration (**a–c**) and CK7 immunocytochemistry (**d**).

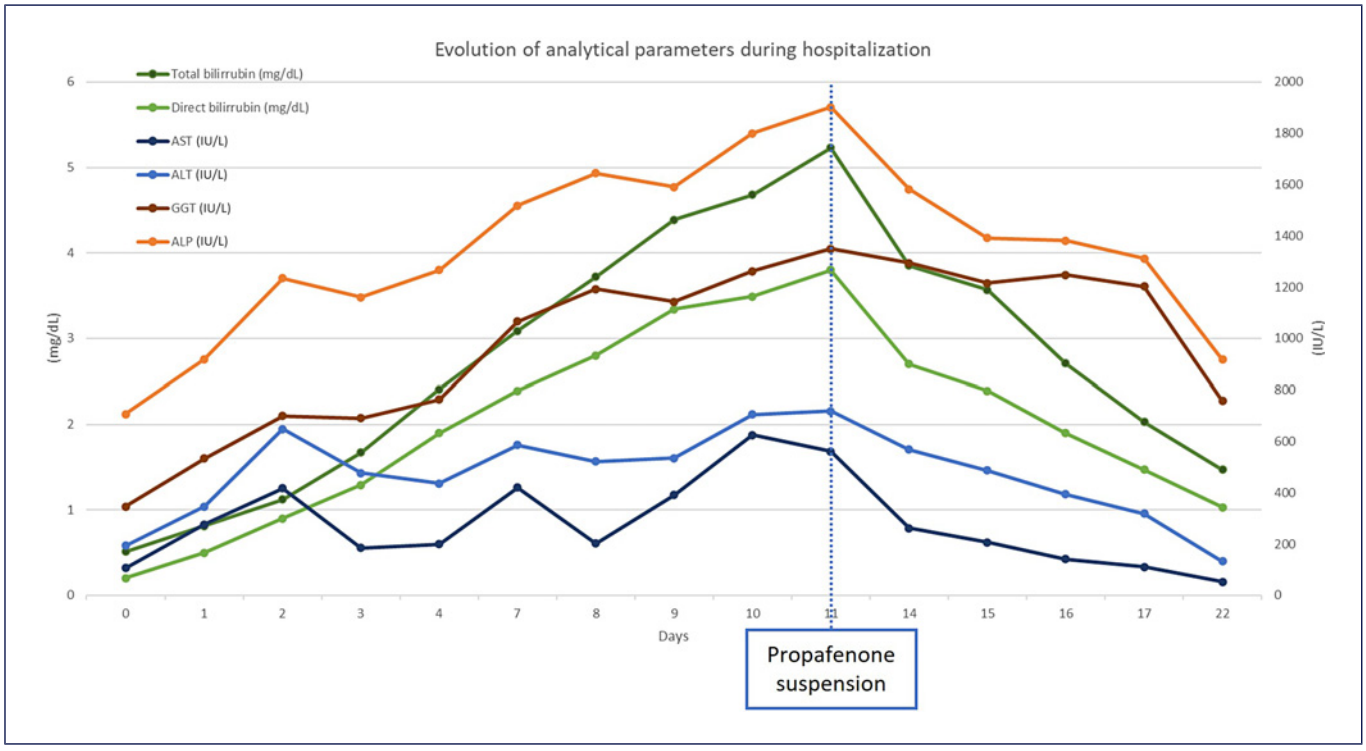

Fig. 4. Evolution of clinical and analytical parameters during hospitalisation.

Table 2. RUCAM score

RUCAM criteria	Points
Time from drug initiation to onset of altered liver tests, between 5 and 90 days	+2
≥50% decrease in ALT within 8 days of drug withdrawal	+3
No alcohol use	0
Age ≥55 years	+1
Concomitant use of levothyroxine, which is considered a likely rare cause of clinically evident liver injury	−1
Exclusion of all alternative causes by: • Anti-HAV IgM, anti-HCV, anti-HEV IgM, anti-HEV IgG, HEV RNA • Imaging studies (hepatobiliary ultrasound, colour Doppler ultrasound of the liver vessels, endoscopic ultrasound, computed tomography, or magnetic resonance) • Alcoholism • History of recent acute hypotension • Complications of underlying disease (sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver disease) • Infection indicated by change in EBV′ VZV, CMV, and HSV titres	+2
Previously published but unlabelled propafenone hepatotoxicity	+1
No unintentional re-exposure	0

ALT, alanine transaminase; HAV, hepatitis A virus; HCV, hepatitis C virus; HEV, hepatitis E virus; EBV, Epstein-Barr virus; VZV, varicella-zoster virus; CMV, cytomegalovirus; HSV, herpes simplex virus.

Our patient developed cholestatic liver injury approximately 2 weeks after starting propafenone, with development of jaundice and pruritus within 3 to 4 weeks thereafter. Three months after withdrawal, the patient was asymptomatic and all liver tests had normalised. Most clinical cases of propafenone-induced DILI report a clinical presentation with cholestatic liver injury, and all cases reported the presence of jaundice, with a latency period generally between 2 and 8 weeks [25–28]. In the reported cases, the jaundice and altered liver tests resolved gradually, within weeks or months after discontinuation of propafenone [3, 25–28]. Propafenone is mainly metabolised by the liver and the accumulation of toxic metabolites, such as p-quinone intermediates, may be involved in propafenone-induced hepatotoxicity [29]. In addition, continuous enterohepatic recirculation may explain the slow clearance of the putative metabolites and the gradual decrease in liver enzymes [26, 29]. Finally, previous case reports of propafenone-induced DILI have described liver biopsies showing portal tract enlargement with infiltrates of lymphocytes, monocytes, macrophages or granulocytes, as well as bile duct proliferation, hepatocyte ballooning and macrovesicular steatosis [3, 25, 26, 28].

In our case, endoscopic ultrasound played an important role in the investigation of cholestatic liver dysfunction with hyperbilirubinemia. This technique allows accurate visualisation of the common bile duct, and in the absence of abnormalities, an endoscopic ultrasound-guided liver biopsy can be performed during the same procedure [30]. However, it is important to note that the number of portal tracts obtained with this method in our case was slightly below the ideal number for liver samples. Magnetic resonance cholangiopancreatography is also an alternative with the advantage of being non-invasive, although it is not widely available and does not allow biopsy to be taken at the same time [31]. Both techniques are valuable in the investigation of cholestatic liver dysfunction, and their use depends on local expertise and availability.

Conclusion

Propafenone is a widely used antiarrhythmic drug, and as hepatotoxicity associated with this drug is very rare, routine monitoring of liver function tests in all patients receiving propafenone cannot be recommended. However, in cases of cholestatic and/or hepatocellular injury, hepatotoxicity related to propafenone should be suspected, justifying its discontinuation. Most clinical cases report a cholestatic liver injury, and all cases had jaundice. Our case is intended to highlight a rare but typical presentation of DILI. When hepatotoxicity is suspected with cholestatic and/or hepatocellular injury, a detailed

medical history is crucial, with assessment of all medications and the temporal relationship with their initiation being key to a prompt diagnosis.

Statement of Ethics

The publication of this case report was approved by the Institutional Review Board in Unidade Local de Saúde do Alto Ave, Guimarães, Portugal (Data Protection Office Statement Reference No. 22/2024). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Data collection was performed by Ana Isabel Ferreira. The first draft of the manuscript was written by Ana Isabel Ferreira. All authors contributed to the case report study conception and design, commented on previous versions of the manuscript, and read and approved the final manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed.

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