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# Possible Semaglutide-Associated Acute Hepatocellular Liver Injury: A Case Report

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## Abstract

Drug-induced liver injury (DILI) is a diagnosis of exclusion that relies on a compatible temporal relationship between drug exposure and liver injury, the course after withdrawal of the suspected agent, and the exclusion of alternative etiologies. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide, are widely prescribed for type 2 diabetes mellitus and obesity, and semaglutide was recently approved for metabolic dysfunction-associated steatohepatitis; clinically significant hepatotoxicity has been reported only rarely. We describe a 56-year-old woman with obesity, without diabetes, who presented to the emergency department with right flank pain 89 days after starting oral semaglutide 3 mg once daily. Aspartate aminotransferase and alanine aminotransferase levels were 14.6 and 10.2 times the upper limit of normal, respectively, with elevated gamma-glutamyl transferase (GGT), mild hyperbilirubinemia, and a normal alkaline phosphatase level (R ratio 11.1, hepatocellular pattern). Serology for hepatitis A, B, C, and E and antinuclear antibodies were negative, creatine kinase was normal, and unenhanced abdominopelvic CT showed no significant biliary dilatation, choledocholithiasis, or features of acute cholecystitis. Semaglutide was discontinued, whereas fluoxetine and clonazepam, started approximately six months earlier, and olmesartan were continued. Liver tests improved progressively, with a 54% reduction in the elevation of alanine aminotransferase above the upper limit of normal (ULN) by day 7. The updated Roussel Uclaf Causality Assessment Method (RUCAM) score was 6 (probable) for semaglutide, 4 (possible) for fluoxetine, and 2 (unlikely) for both clonazepam and olmesartan, and the injury was graded as mild. Transient biliary obstruction could not be completely excluded, as the abdominal ultrasound result and laboratory follow-up beyond day 7 were not available. This case suggests that semaglutide should be considered in the differential diagnosis of unexplained hepatocellular liver injury and highlights the need for a structured causality assessment that includes the exclusion of biliary disease, a recognized complication of this drug class.

**Categories:** Pharmacology, Internal Medicine, Gastroenterology
**Keywords:** choledocholithiasis, drug-induced liver injury, glucagon-like peptide-1 receptor agonist, hepatocellular liver injury, hepatotoxicity, pharmacovigilance, rucam score, semaglutide

## Introduction

Drug-induced liver injury (DILI) is an uncommon but clinically important adverse drug reaction, with a population-based annual incidence of approximately 19 cases per 100,000 inhabitants, and it is a leading cause of acute liver failure in Western countries [1-3]. DILI is broadly classified as intrinsic, which is predictable and dose-dependent, or idiosyncratic, which occurs unpredictably in a small proportion of exposed individuals and results from the interaction between drug properties, host genetic and metabolic factors, and adaptive immune responses directed against hepatocytes or cholangiocytes [1,2]. Its clinical spectrum ranges from asymptomatic elevation of liver tests to acute hepatitis, prolonged cholestasis, acute liver failure, and chronic liver injury, and the biochemical pattern is classified as hepatocellular, cholestatic, or mixed according to the R ratio [1,2].

Because no specific biomarker is available, DILI remains a diagnosis of exclusion, based on a compatible temporal relationship between drug exposure and the onset of liver injury, the course following withdrawal of the suspected agent, and the exclusion of alternative etiologies, including viral, autoimmune, ischemic, metabolic, and biliary causes [1,2]. Structured causality assessment tools, such as the updated Roussel Uclaf Causality Assessment Method (RUCAM), help standardize this process, and the cornerstone of management is the prompt withdrawal of the suspected agent [2,4].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide, are widely used in the management of type 2 diabetes mellitus and obesity and generally exhibit a favorable hepatic safety profile [5]. Semaglutide has demonstrated histological benefits in metabolic dysfunction-associated steatohepatitis (MASH) [6,7], and subcutaneous semaglutide 2.4 mg received accelerated approval from the US Food and Drug Administration in August 2025 for non-cirrhotic MASH with moderate-to-advanced fibrosis [8]. In this context, a hepatotoxicity signal is unexpected and therefore noteworthy. Nevertheless, a small number of cases of semaglutide-associated DILI have been reported, with heterogeneous patterns and severity [9-14]. In addition, GLP-1 RAs increase the risk of gallbladder and biliary disease [15], which must be distinguished

from direct hepatocellular injury. We report a case of acute hepatocellular liver injury in a patient receiving oral semaglutide, with a structured causality assessment and an explicit discussion of transient biliary obstruction as the main alternative diagnosis.

## Case Presentation

A 56-year-old White woman with obesity and a history of left nephrolithiasis, complicated by recurrent urinary tract infections and episodes of pyelonephritis, had previously undergone extracorporeal shock wave lithotripsy and ureteral stent placement. Renal scintigraphy revealed a hypofunctioning left kidney, with a differential renal function of approximately 5%, and she underwent left nephrectomy approximately one year before the current presentation, with preserved renal function thereafter. She did not have diabetes mellitus (glycated hemoglobin 5.2%). No liver tests performed before the initiation of semaglutide were available.

Oral semaglutide 3 mg once daily had been prescribed by her attending physician for the treatment of obesity, an off-label indication, and had been taken at a constant dose, without escalation, for 89 days before presentation. According to the patient, her body weight decreased from 94 kg at initiation to 91 kg at presentation, a loss of approximately 3 kg (3.2%); height and body mass index were not recorded. Concomitant medications included olmesartan 20 mg daily, taken for several months, and fluoxetine 20 mg daily and clonazepam 0.5 mg, both prescribed for anxiety and started approximately six months before presentation, that is, approximately three months before semaglutide initiation. The patient reported an episode of urinary tract infection approximately two months before presentation, treated with nitrofurantoin; the dates and duration of this course could not be confirmed in the clinical records. No other antibiotics, antibiotic prophylaxis, paracetamol, or nonsteroidal anti-inflammatory drugs were documented in the preceding three months. She denied alcohol consumption and the use of herbal products, dietary supplements, or green tea extracts, reporting only the occasional consumption of chamomile tea.

She presented to the emergency department with right flank pain of sudden onset, which had started approximately two days earlier and was described as a dull ache radiating to the back, without associated nausea, vomiting, or fever. On physical examination, she was alert, oriented, and cooperative, eupneic at rest on room air, and afebrile, with a body temperature of 36.2 °C, a heart rate of 63 beats per minute, and a peripheral oxygen saturation of 98%. There was tenderness on palpation of the right costal margin, costovertebral angle percussion tenderness was absent, and Murphy's sign was equivocal.

Laboratory investigations at presentation revealed a marked elevation in aminotransferases, with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels 14.6 and 10.2 times the upper limit of normal (ULN), respectively, together with elevated gamma-glutamyl transferase (GGT), mild hyperbilirubinemia, and an alkaline phosphatase (ALP) level within the reference range (Table *1*). The calculated R ratio, defined as (ALT/ULN)/(ALP/ULN), was 11.1, consistent with a hepatocellular pattern of liver injury. The international normalized ratio (INR) was mildly elevated at 1.4, whereas albumin, creatinine, lipase, creatine kinase (CK), and C-reactive protein were within the reference ranges. The complete blood count was within the reference ranges, with no eosinophilia.

| Parameter | Day 0 | Day 3 | Day 5 | Day 7 | Reference range |
|---|---|---|---|---|---|
| Aspartate aminotransferase, U/L (× ULN) | 467 (14.6) | 358 (11.2) | 243 (7.6) | 155 (4.8) | <32 |
| Alanine aminotransferase, U/L (× ULN) | 338 (10.2) | 306 (9.3) | 251 (7.6) | 172 (5.2) | <33 |
| Alkaline phosphatase (U/L) | 119 | 125 | 119 | 112 | 40-129 |
| Gamma-glutamyl transferase (U/L) | 140 | 143 | 131 | 115 | 8-78 |
| Total bilirubin (mg/dL) | 1.61 | 1.75 | 1.49 | 1.15 | 0.1-1.0 |
| Conjugated bilirubin (mg/dL) | 0.89 | 0.95 | 0.75 | 0.50 | 0-0.3 |
| International normalized ratio | 1.4 | 1.3 | 1.2 | 1.0 | 0.8-1.2 |
| Albumin (g/dL) | 4.7 | 4.6 | 4.5 | 4.6 | 3.5-5.5 |
| Hemoglobin (g/dL) | 13.9 | 14 | 13.9 | 13.8 | 12-16 |
| Leukocytes (× $10^3$/μL) | 4.8 | 4,9 | 4,8 | 4,8 | 4.5-11.0 |
| Neutrophils (%) | 59.8 | 58,2 | 59 | 59,3 | 54-62 |
| Lymphocytes (%) | 27.1 | 27.3 | 27 | 27 | 25-33 |
| Eosinophils (%) | 2 | 1.98 | 1.7 | 2 | 1-3 |
| Platelets (× $10^3$/μL) | 285 | 286 | 285 | 285 | 150-400 |
| Creatinine (mg/dL) | 0.90 | 0.92 | - | 0.89 | 0.6-1.2 |
| Lipase (U/L) | 44 | - | - | - | 13-60 |
| Creatine kinase (U/L) | 56 | 52 | - | - | 10-70 |
| C-reactive protein (mg/L) | 9.8 | 7.9 | - | 5.4 | <10 |

**TABLE 1: Laboratory findings at presentation and during follow-up**

Legend: Day 0 corresponds to the day of presentation and semaglutide withdrawal. Values in parentheses are multiples of the upper limit of normal (ULN). The R ratio was 11.1

Serological testing for hepatitis A, B, C, and E and antinuclear antibodies were negative, and ferritin, transferrin saturation, and thyroid-stimulating hormone were within the reference ranges (Table *2*). Serology for cytomegalovirus, Epstein-Barr virus, and herpes simplex virus, anti-smooth muscle antibodies, and serum immunoglobulin G were not determined.

| Test | Result | Reference range |
|---|---|---|
| IgM anti-hepatitis A virus | Negative | Negative |
| Hepatitis B surface antigen | Negative | Negative |
| IgM anti-hepatitis B core antigen | Negative | Negative |
| Anti-hepatitis C virus antibodies | Negative | Negative |
| IgM anti-hepatitis E virus | Negative | Negative |
| Antinuclear antibodies | Negative | Negative |
| Ferritin (ng/mL) | 50 | 12-150 |
| Transferrin saturation (%) | 42 | 15-50 |
| Thyroid-stimulating hormone (μU/mL) | 2.3 | 0.5-5.0 |
| Creatine kinase (U/L) | 56 | 10-70 |
| Cytomegalovirus, Epstein-Barr virus, and herpes simplex virus serology | Not determined | - |
| Anti-smooth muscle antibodies and serum immunoglobulin G | Not determined | - |

**TABLE 2: Etiological work-up**

IgM: immunoglobulin M.

Unenhanced abdominopelvic computed tomography (CT) was performed as the initial imaging study, as ultrasonography was not available at the time of presentation; CT also allowed evaluation of the urinary tract in a patient with a solitary right kidney and a history of nephrolithiasis. It revealed a liver of normal size with regular contours and a globally homogeneous parenchyma. A single 8 mm hypodense lesion was identified in segment II, consistent with a small simple hepatic cyst. There was no intrahepatic biliary dilatation, and the common bile duct measured up to 7 mm in diameter, which was not considered dilated by the radiologist. No calculi were identified in the gallbladder or bile ducts. The gallbladder was distended, with a maximum transverse diameter of 4.2 cm, but showed no wall thickening, pericholecystic fat stranding, or edema, and therefore did not fulfill the CT criteria for acute cholecystitis (Figure *1*). The pancreas showed no relevant abnormalities, and there were no right renal or ureteric calculi and no hydronephrosis.

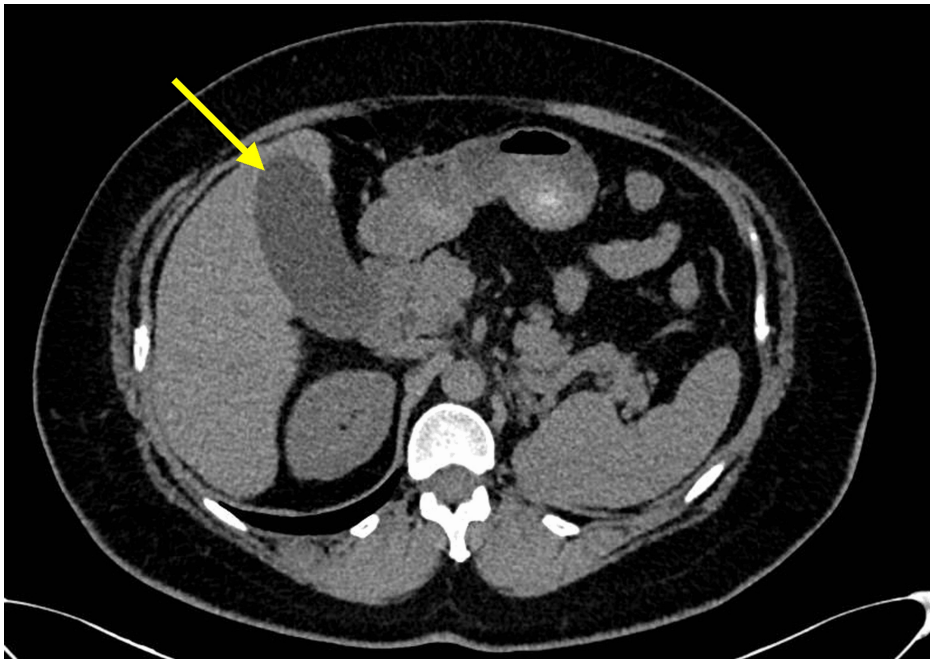


**FIGURE 1: Axial unenhanced abdominopelvic computed tomography showing a liver of normal size with homogeneous parenchyma and a distended gallbladder (arrow), without wall thickening, pericholecystic fat stranding, or edema**

Given the presence of acute hepatocellular liver injury and the absence of imaging findings suggestive of biliary obstruction or other acute hepatobiliary disease, the case was discussed with the gastroenterology team. DILI was considered the leading diagnostic hypothesis, with a possible association with semaglutide. Semaglutide was discontinued on the day of presentation, whereas fluoxetine, clonazepam, and olmesartan were continued. The pain was ultimately attributed to a musculoskeletal cause.

Liver tests improved progressively after semaglutide withdrawal (Table *1*, Figure *2*). ALT decreased from 338 U/L at presentation to 306, 251, and 172 U/L on days 3, 5, and 7, corresponding to reductions of 9.5%, 25.7%, and 49.1% in absolute values and of 10.5%, 28.5%, and 54.4% in the elevation above the ULN. AST decreased by 66.8%, from 467 to 155 U/L, by day 7. Total bilirubin, GGT, and ALP were slightly higher on day 3 and decreased thereafter, with ALP remaining within the reference range throughout, and the INR normalized to 1.0 by day 7. With total bilirubin below twice the ULN and an INR below 1.5, the injury was graded as mild. Abdominal ultrasonography and further laboratory monitoring were requested; however, the ultrasound result and laboratory values after day 7, including the time to complete normalization, were not accessible to the authors. The case is being reported to the Portuguese national pharmacovigilance authority (INFARMED).

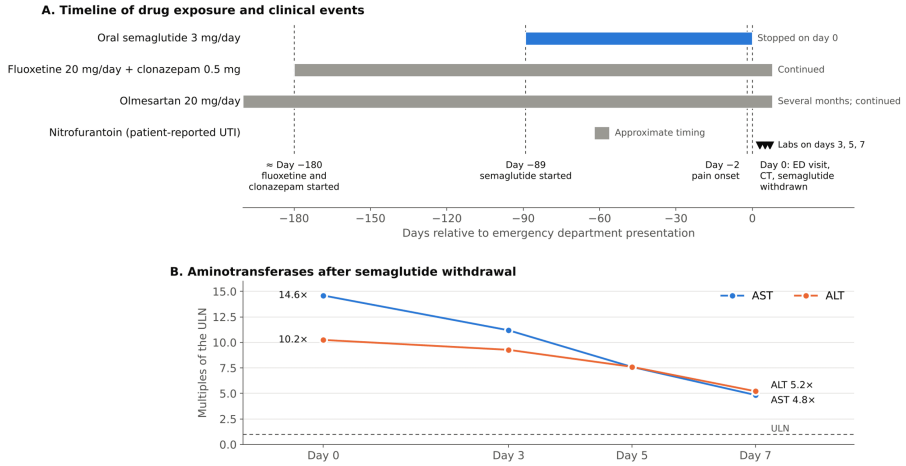



**FIGURE 2: Timeline of drug exposure, clinical events, and aminotransferase course**

(A) Drug exposure and clinical events relative to the day of presentation (day 0). (B) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT), expressed as multiples of the upper limit of normal (ULN), after semaglutide withdrawal.

ED: emergency department, CT: computed tomography, UTI: urinary tract infection.

## Discussion

In the present case, the R ratio of 11.1 at presentation and 9.6 on day 3, classified the injury as hepatocellular [1,2]. According to the International DILI Expert Working Group criteria, the injury was mild, as ALT exceeded five times the ULN while total bilirubin remained below twice the ULN and the INR below 1.5, and Hy's law was not met [16].

Semaglutide undergoes limited hepatic metabolism and, in clinical trials, has not been associated with clinically relevant elevations in aminotransferases [5]; it has instead demonstrated beneficial effects on hepatic steatosis, inflammation, and fibrosis [6,7]. Most hepatobiliary complications reported with GLP-1 RAs consist of cholelithiasis, cholecystitis, or choledocholithiasis, rather than direct hepatocellular injury [15]. Nevertheless, rare cases of semaglutide-associated DILI have been published, with latencies ranging from two weeks to several months, hepatocellular, cholestatic, or mixed patterns, and outcomes ranging from spontaneous resolution to acute liver failure and liver transplantation [9-14] (Table *3*). Of note, oral semaglutide is co-formulated with the absorption enhancer salcaprozate sodium (SNAC) [17], and the case reported by the Drug-Induced Liver Injury Network also involved the oral formulation [9]; however, any contribution of SNAC to liver injury is purely speculative and cannot be inferred from isolated reports.

| Case | Age (years), sex | Formulation and dose | Latency | Pattern (R ratio) | Causality | Outcome |
|---|---|---|---|---|---|---|
| Enslin et al. (2021) [10] | 79, male | Not reported | 6 weeks | Mixed, autoimmune-like (3.6) | RUCAM 6 | Resolution after withdrawal |
| Ma et al. (2022) [9] | 51, male | Oral, 3 mg then 7 mg daily | 27 days | Cholestatic (0.6) | RUCAM 3; DILIN probable | Biliary cirrhosis; liver-kidney transplantation |
| Galeano Lovera and Gnanapandithan (2023) [11] | 67, female | Not reported | 2 weeks | Hepatocellular (16.5) | RUCAM 7 | Resolution after withdrawal |
| Kalsi et al. (2025) [14] | 44, female | Subcutaneous, 1 mg weekly | 4 weeks | Hepatocellular (37) | RUCAM 8; positive rechallenge | Resolution after withdrawal |
| Present case | 56, female | Oral, 3 mg daily | 89 days | Hepatocellular (11.1) | RUCAM 6 | Improving at day 7; later follow-up not available |

**TABLE 3: Published cases of semaglutide-associated liver injury compared with the present case**

Note: Data for previously published cases are taken from the original reports and from the summary by Kalsi et al. [14].

RUCAM: Roussel Uclaf Causality Assessment Method; DILIN: Drug-Induced Liver Injury Network.

Causality was assessed using the updated RUCAM, applied separately to each suspect drug [4] (Table *4*). For semaglutide, the latency of 89 days was compatible, and the elevation of ALT above the ULN decreased by 54.4% within eight days of withdrawal, corresponding to the highest dechallenge score, resulting in a total score of 6 (probable). Fluoxetine scored 4 (possible), and clonazepam and olmesartan each scored 2 (unlikely). Fluoxetine is a recognized, albeit rare, cause of clinically apparent liver injury, whereas clonazepam has only rarely been implicated [18]; both had been taken for approximately six months, including three months before semaglutide initiation, a longer latency that does not exclude, but makes less likely, their involvement. However, liver tests improved despite the continuation of fluoxetine, clonazepam, and olmesartan, which represents the strongest argument in favor of semaglutide as the causative agent [2]. Nitrofurantoin, reportedly taken approximately two months before presentation, was considered unrelated, because liver injury began more than 15 days after the cessation of this rapidly eliminated drug [4].

| RUCAM item | Semaglutide | Fluoxetine | Clonazepam | Olmesartan |
|---|---|---|---|---|
| 1. Time to onset from the beginning of the drug | +2 (89 days) | +1 (approximately 6 months) | +1 (approximately 6 months) | +1 (several months) |
| 2. Course of ALT after cessation | +3 (54.4% decrease within 8 days) | 0 (continued) | 0 (continued) | 0 (continued) |
| 3. Risk factors (age ≥55 years; no alcohol use) | +1 | +1 | +1 | +1 |
| 4. Concomitant drugs | -2 (fluoxetine) | -1 (semaglutide) | -2 (fluoxetine) | -2 (fluoxetine) |
| 5. Search for alternative causes (all group I causes excluded) | +1 | +1 | +1 | +1 |
| 6. Previous information on hepatotoxicity | +1 (published, unlabeled) | +2 (labeled) | +1 (published) | +1 (published) |
| 7. Response to unintentional re-exposure | 0 | 0 | 0 | 0 |
| Total score (causality grade) | 6 (probable) | 4 (possible) | 2 (unlikely) | 2 (unlikely) |

**TABLE 4: Updated RUCAM scores for each suspect drug**

Note: Item 2 is based on the percentage decrease in the difference between the peak ALT value and the ULN.

Group I causes: hepatitis A, B, C, and E, hepatobiliary imaging, alcohol use, and recent hypotension.

Causality grades: ≤0, excluded; 1-2, unlikely; 3-5, possible; 6-8, probable; ≥9, highly probable.

RUCAM: Roussel Uclaf Causality Assessment Method, ALT: alanine aminotransferase, ULN: upper limit of normal.

The main alternative diagnosis is transient biliary obstruction due to the spontaneous passage of a common bile duct stone or sludge. Choledocholithiasis may present with marked aminotransferase elevation, exceeding 500 U/L in approximately one-third of patients [19], and GLP-1 RAs increase the risk of gallbladder and biliary disease [15]. In that scenario, liver injury would still be related to semaglutide, but through a biliary mechanism rather than idiosyncratic hepatotoxicity. Right-sided pain, right costal margin tenderness, an equivocal Murphy's sign, a distended gallbladder, elevated GGT and conjugated bilirubin, and AST predominance at presentation are compatible with this hypothesis. However, several findings favor hepatocellular DILI. ALP remained within the reference range on all four measurements; there was no intrahepatic biliary dilatation, the common bile duct was not considered dilated, and no calculi were visible; lipase was normal; the pain was located in the flank, radiated to the back, and was attributed to a musculoskeletal cause; and weight loss was modest, at approximately 3%, whereas rapid weight loss is a recognized risk factor for gallstone formation. Furthermore, aminotransferases declined gradually over one week, with ALT decreasing by only 9.5% by day 3, rather than abruptly, as usually observed after the resolution of a transient obstruction. A normal CK excluded a muscular source of AST. Nevertheless, because unenhanced CT has limited sensitivity for non-calcified stones and the ultrasound result was not available, transient biliary obstruction cannot be completely excluded.

This report has several limitations. The ultrasound result was not accessible, and magnetic resonance cholangiopancreatography or endoscopic ultrasound was not performed. Laboratory follow-up after day 7, and therefore the time to complete normalization, was not available. Serology for cytomegalovirus, Epstein-Barr virus, and herpes simplex virus, anti-smooth muscle antibodies, and serum immunoglobulin G were not determined, and no liver biopsy was performed. Liver tests obtained before semaglutide initiation were not available, so pre-existing steatotic liver disease cannot be excluded. The nitrofurantoin course was patient-reported and could not be verified. Finally, given the elimination half-life of semaglutide of approximately one week [17], biochemical improvement began while the drug was still present in plasma, which limits the interpretation of the dechallenge. Despite these limitations, the temporal relationship, the hepatocellular pattern, the exclusion of viral, autoimmune, metabolic, and muscular causes, and the improvement after semaglutide withdrawal despite continuation of the other drugs support a possible association with semaglutide. Given its increasing use, clinicians should consider this rare adverse reaction in patients with unexplained liver test abnormalities, perform a thorough medication review, actively exclude biliary disease, and report suspected cases to pharmacovigilance systems.

## Conclusions

This case describes acute hepatocellular liver injury occurring approximately three months after the

initiation of oral semaglutide, with progressive biochemical improvement after drug withdrawal despite the continuation of other potentially hepatotoxic medications. A structured causality assessment supported a probable association with semaglutide, although transient biliary obstruction could not be completely excluded, and we therefore consider the association possible.

Given the expanding use of semaglutide in type 2 diabetes mellitus, obesity, and steatohepatitis, clinicians should be aware that this agent, while generally considered safe for the liver, may rarely be associated with hepatocellular injury. In patients presenting with unexplained liver test abnormalities, a careful medication review, the systematic exclusion of alternative etiologies, including biliary disease, the application of a structured causality assessment, and the prompt discontinuation of the suspected agent are essential. Reporting such cases to pharmacovigilance systems contributes to a better characterization of the hepatic safety profile of this drug class.

# Additional Information

## Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Andreia Freitas, Cláudia Abreu Rocha

**Acquisition, analysis, or interpretation of data:** Andreia Freitas, Cláudia Abreu Rocha

**Drafting of the manuscript:** Andreia Freitas, Cláudia Abreu Rocha

**Critical review of the manuscript for important intellectual content:** Andreia Freitas, Cláudia Abreu Rocha

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