Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

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DOI: 10.17235/reed.2025.11064/2025
Link: PubMed (Epub ahead of print)

Please cite this article as:
Pichel Rita Carrilho, Miranda Hugo Miguel, Sá Diogo Carvalho, Coelho João Queirós, Lopes Pedro Lemos, Ramos Maria João, Viscaíno José Ramón, Araújo António. Histologic findings of liver injury during pembrolizumab-axitinib treatment. Rev Esp Enferm Dig 2025. doi: 10.17235/reed.2025.11064/2025.

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Histologic findings of liver injury during pembrolizumab-axitinib treatment

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Keywords: Axitinib. Pembrolizumab. Acute liver injury. Liver histology.

Dear Editor,

Hepatotoxicity is a significant concern in systemic cancer treatments. The pembrolizumab-axitinib combination, used in advanced renal cell carcinoma (RCC), is associated with a 22% incidence of ≥G3 liver enzyme elevations. In this case report we provide the first description of liver biopsy findings of axitinib or pembrolizumab-axitinib drug-induced liver injury (DILI). These findings may enhance understanding of the hepatotoxic effects of this combination and inform strategies for patient management.

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Case report

A 69-year-old man presented with diarrhea, coluria, malaise, anorexia and tremor. His medical history included metastatic clear cell RCC, receiving first-line systemic treatment with pembrolizumab-axitinib for 6 months, with partial response. Treatment-related adverse events included G2 hepatitis. Additional comorbidities included systemic hypertension, stage 3 chronic kidney disease and paraneoplastic polycythemia.

At physical examination he presented confusion, jaundice and fluid-responsive hypotension. Diagnostic testing showed G4 liver enzyme elevation (>20ULN ALT increase), with G2 hyperbilirubinemia, G2 cholestasis and slight prolongation of prothrombin time, G1 acute kidney injury (AKI), aggravation of polyglobulia and G1 thrombocytopenia. Inflammatory parameters, albumin and ionic profile were normal.

The primary working diagnosis was iatrogenic acute hepatitis. An abdominopelvic CT scan showed no signs of thrombosis or RCC progression. Infectious and autoimmune causes were excluded. Axitinib was discontinued and intensive fluid therapy, high-dose corticosteroids (IV-methylprednisolone 2mg/kg) and vitamin K were initiated, with resolution of symptoms and return of hepatitis to G2. Tapering of corticosteroids began after 5 days.

Multidisciplinary meeting of toxicities proposed a liver biopsy to attempt an identification of the culprit agent. Ten days after presentation the patient underwent an uncomplicated liver biopsy (Figure 1). He was later discharged, asymptomatic and with G1 hepatitis that did not recur on corticosteroid tapering.

Discussion

We believe the primary cause of liver injury in this case was axitinib toxicity as a DILI. Although the mechanism of action for axitinib-induced hepatotoxicity remains undefined,(1) the pathological findings of necroinflammation suggest a pauci-inflammatory mechanism of liver injury and resemble those reported with other VEGFR-TKI.(2, 3) Ischemic hepatitis most likely also played a role, supported by the presence of hypovolemia; however, the disproportionate elevation of liver enzymes compared to mild AKI argues against it being the predominant factor.

Concurrent mechanisms of liver toxicity, including pembrolizumab-induced immunotoxicity, cannot be excluded based solely on the biopsy findings (conducted after 10 days of corticosteroid therapy). DILI due to immune-checkpoint inhibitors is reviewed elsewhere. (4) The absence of systemic inflammation markers makes pembrolizumab a less likely culprit; however, its potential synergism cannot be excluded, which may explain the higher liver toxicity observed with pembrolizumab-axitinib compared to monotherapy with either agent.(5, 6)

The greatest limitation of this report is that the patient was treated with anti-inflammatory drugs before the biopsy, potentially suppressing immune response in the liver tissue. Nevertheless, to our knowledge, this case report first describes the pathological findings of DILI in a patient undergoing pembrolizumab-axitinib.

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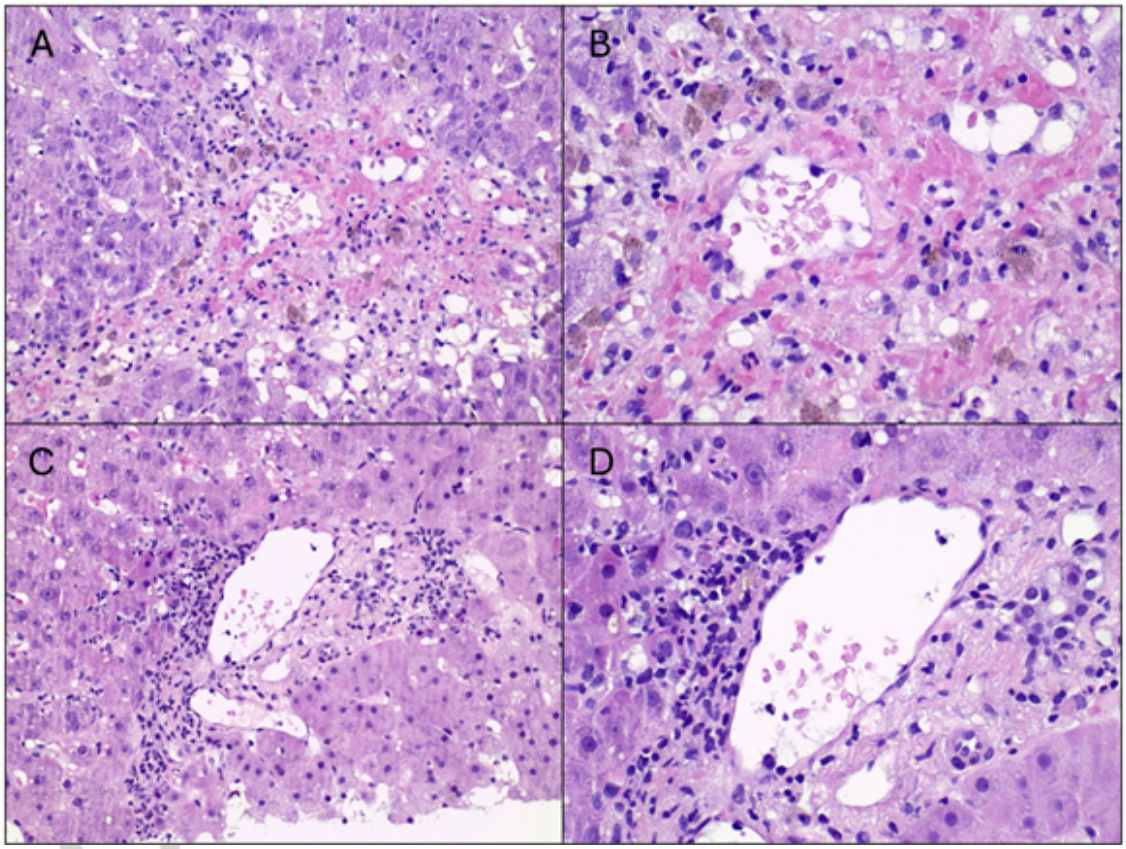

Figure 1. Liver biopsy. Pericentrovenular hepatocellular necrosis (Panels A and B, H&E 200x and 400x) – these findings indicate an ischemic injury. Polymorphic inflammatory infiltrate in portal spaces with necroinflammatory activity at the interface (Panels C and D, H&E 200x and 400x) – this pattern of injury can be attributed to drug toxicity.