Despite advances in the understanding and in assessing causality in DILI, it is necessary to rely heavily on clinical judgement and expert input when making decisions regarding the likely cause of an acute liver injury.[9] A thorough examination of the circumstances of the liver injury include: defining a clear time of onset (latency) and response to withdrawal, confirming the absence of risk factors predisposing to other possible causes and using histology in unpredictable and/or unclear cases. All these strategies are the main tools to corroborate a high index of suspicion and to define, as in this case, the causality of a drug induced liver injury.

Acknowledgments and potential conflicts of interest

None declared.

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Significantly elevated CA 19-9 levels in a patient with choledocholithiasis☆

Coledocolitiasis como causa de elevación importante del marcador tumoral CA 19-9

CA 19-9 is a carbohydrate antigen commonly used as a tumour marker in pancreatic neoplasms. It is a tool that supports diagnosis, detects recurrence in treated neoplasms and monitors treatment response, though it is not useful in pancreatic carcinoma screening. Although very marked elevations require discarding a neoformative process of this type as the first possibility in a patient with obstructive jaundice, cases of extreme marker elevation have been described in benign bile duct disease.[1]

We present the case of a 69-year-old female patient with a significant smoking and alcohol habit. She came to the Emergency Department after a week of progressive epigastric pain, radiating at the waist, which worsens with ingestion, and jaundice; with no fever or weight loss. In the physical examination only the mucocutaneous jaundice mentioned above was notable, with the abdominal examination being anodyne. In the blood tests she had a total bilirubin of 41.07 mg/dl (normal values: 0.2–1.2 mg/dl), AST 371 U/l (4–50 U/l), ALT 568 U/l (5–40 U/l), GGT 2590 U/l (10–50 U/l), LDH 324 U/l (140–250 U/l), ALP 757 U/l (53–128 U/l), normal amylase and lipase, CRP 24 mg/l (0–5 mg/l) and leukocytosis. She was admitted with suspected biliopancreatic carcinoma as the first possibility. In later examinations, a CA 19-9 > 12,000 IU/ml (0–37 IU/ml) was notable, with normal carcinoembryonic antigen (CEA). In the abdominal ultrasound, choledocholithiasis was observed, with intrahepatic and extrahepatic biliary dilatation, as well as stones in the gallbladder and pancreatic parenchyma without alterations. The abdominal CT and echo-endoscopy confirmed the suspicion of distal choledocholithiasis with dilatation of the bile duct (Figs. 1 and 2), gallstones and a pancreatic parenchyma, without alterations. Spontaneously, 48 h after admission, she also presented a drop in total bilirubin and CA 19-9, at 19.77 mg/dl and 1473 IU/ml, respectively. ERCP was performed with a sphincterotomy, with the goal of removing large gallstones and biliary sludge. Bilirubin levels gradually

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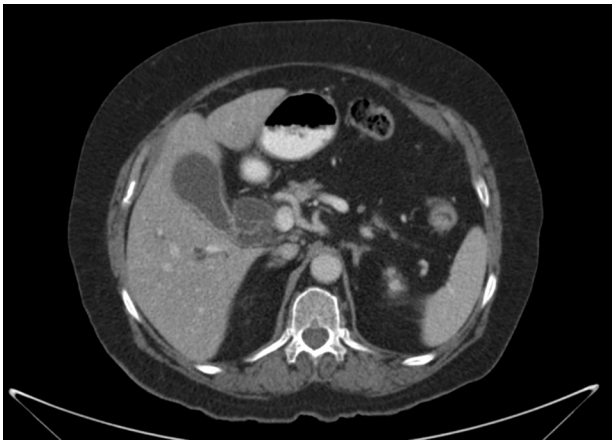

Figure 1 Dilatation of the extrahepatic bile duct in the abdominal CT. Significant dilation of the extrahepatic bile duct is observed, due to obstruction in the distal common bile duct. The intrahepatic bile duct is slightly dilated in some areas, in a liver with regular contours, with no radiological data of chronic liver disease.

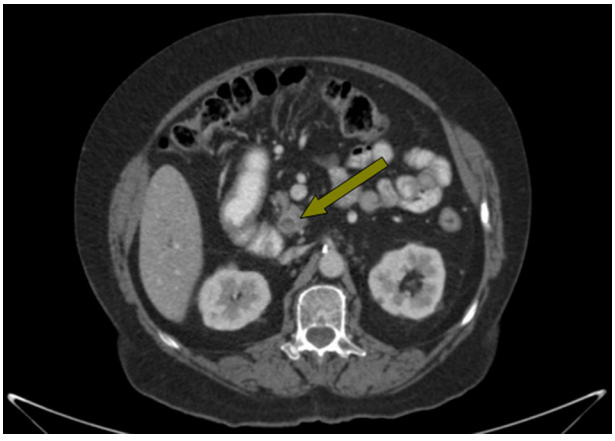

Figure 2 Distal choledocholithiasis. Abdominal CT scan, where gallstones are observed in the distal end of the bile duct, which conditions the retrograde dilatation of the extrahepatic duct, without identifying abnormalities in the pancreatic cephalic portion.

declined in line with the CA 19-9 levels, with concentrations reaching 10.13 mg/dl and 366.4 IU/ml, respectively, on discharge. One month after discharge, CA 19-9 was 22 IU/ml and no pancreatic or biliary tract disease was detected in imaging tests. Subsequently, the patient has undergone a programmed cholecystectomy.

CA 19-9 is a carbohydrate antigen, related to the Lewis blood group antigen, which was first isolated by monoclonal antibodies in a culture of human colorectal neoplastic cells.[2] It is synthesized by various normal epithelia of the organism, such as pancreatic or biliary, among others. Initially used as a colorectal tumour marker, it is now widely used as a tumour marker associated with pancreatic carcinoma, although it may be elevated in other neoplastic processes such as gastric, oesophageal or ovarian tumours,[3] with elevations above 37–40 IU/ml considered abnormal. High levels can also be found in benign diseases, such as acute cholangitis, cholestatic processes, pancreatitis, cirrhosis and some forms of autoimmune thyroiditis.[4,5] Although the figures found in cases of benign disease are usually lower than in malignant ones, some authors believe that, by establishing the appropriate cut-off point, the marker may be useful in differentiating benign and malignant pancreatic disease, if combined with radiological assessment.[6] Thus, a value above 1000 IU/ml generally indicates the presence of a malignant digestive neoplasm, with a specificity greater than 99% for pancreatic carcinoma.[7] However, the possibility of false positives has to be taken into account, since extremely high levels of the marker can also be found in cases of benign disease. Several cases have been reported in the literature of significant elevation of the marker in biliary obstructive disease.[8,9] In a series of 70 patients with choledocholithiasis, 32 of them (46%) had a CA 19-9 elevation with an average value of 300 IU/ml and a maximum value of 2000 IU/ml.[10] The mechanism through which the marker levels are raised in these cases is not completely clear, although it is believed the following elements could play a part: (1) its production exacerbated by irritated epithelial cells due to the increase of intrabiliary pressure, and (2) the accumulation of the marker in the bile duct due to obstruction, with reflux into the bloodstream. In cases of malignant disease, however, the normalization of the marker is more conditioned by the resection of the tumour than by the unblocking of the pathway.

The presented case reflects this type of situation as, after the drainage of the bile duct, the patient's test parameters (mainly bilirubin and CA 19-9) decreased within one month until their complete normalization. Moreover, no neoplasms were observed after the imaging tests, with the patient remaining asymptomatic one month after hospital discharge. Consequently, the finding of extremely high levels of CA 19-9 in a patient with obstructive jaundice must be interpreted with caution. The isolated determination of the marker, without an adequate clinical context, can lead to costly and unnecessary examinations. Although in these cases the first diagnostic option to be considered is a malignant disease, the possibility of benign disease should not be ruled out by the results obtained in an isolated determination.

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