Inflammatory myofibroblastic tumor of the liver mimicking Klatskin tumor☆

Tumor miofibroblástico inflamatorio hepático que mimetiza un tumor de Klatskin

Cholangiocarcinoma is the most common malignant neoplasm of the bile duct. It is an aggressive cancer whose only potentially curative treatment is surgery. Depending on its location, cholangiocarcinoma is classified as intrahepatic, distal and perihilar or Klatskin tumor. Given the low cost-effectiveness of preoperative cytological studies, the indication for surgical treatment is usually based on clinical and radiological findings. Despite this, up to 15% of biliary strictures may be associated with other pathological processes, a fact that often cannot be corroborated until the definitive pathological study is completed[1].

In this context, we present the case of a 37-year-old male patient who was admitted due to painless jaundice, pruritus and asthenia that had been progressing over the previous 2 weeks. His medical history of interest included a tobacco habit of 10 pack-years and laparoscopic surgery for acute appendicitis one year before the onset of the current symptoms. Lab work-up showed the following values: total bilirubin 3.8 mg/dL, direct bilirubin 3.1 mg/dL, GOT 87 U/L, GGT 356 U/L, alkaline phosphatase 227 U/L, slight leukocytosis, and negative tumor markers (CEA and CA 19.9). Imaging tests (thoracic-abdominal-pelvic CT scan and hepatic and magnetic resonance cholangiopancreatography [MRCP]) show a mass infiltrating the left hepatic duct with dilatation of the ipsilateral intrahepatic bile duct (Fig. 1, images A and B), with no distant disease. These findings suggested a type IIIb Klatskin tumor as the first possible diagnosis[1]. Surgical treatment was decided after

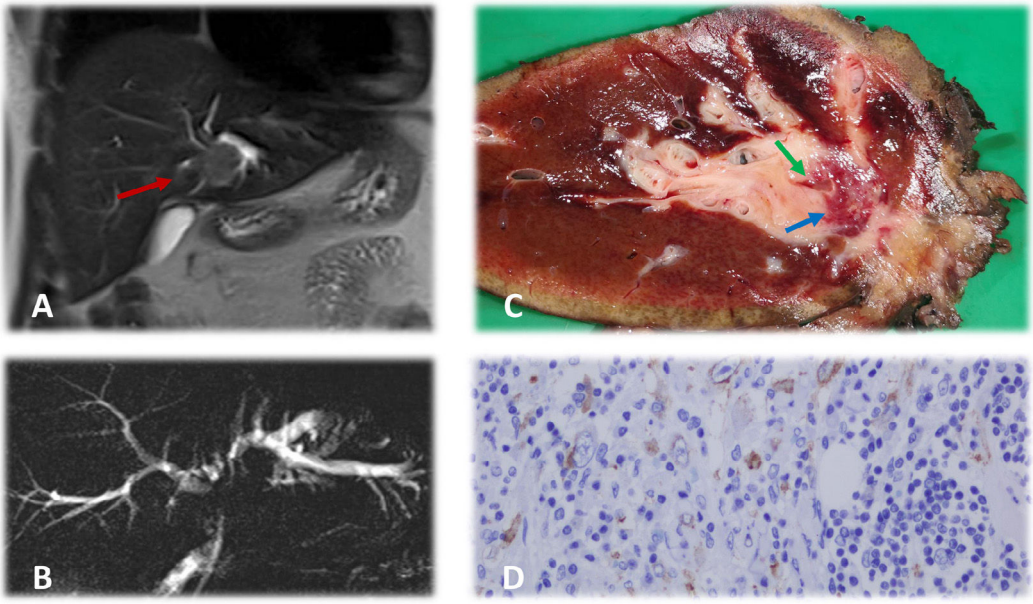

Fig. 1 – A) Hepatic magnetic resonance study showing a mass that is neoplastic in appearance (red arrow) in the perihilar area, infiltrating the left hepatic duct and causing dilation. B) Nuclear magnetic resonance cholangiography showing notable dilation of the left intrahepatic bile duct and, to a lesser degree, of the right bile duct. Radiological 'silence' is observed at the bifurcation of both hepatic ducts secondary to the tumor. The common bile duct presents a normal diameter. C) Macroscopic image of the hepatectomy piece. A 2.3 × 1.9 cm lesion (blue arrow) is observed, partially encompassing the bile duct (green arrow) with a surrounding inflammatory reaction. D) Microscopic image of the hepatectomy specimen. The mass is mainly formed by a loose stroma with epithelioid cells, evident nucleoli and areas of more fasciculated distribution. Both areas present an inflammatory infiltrate comprised of lymphocytes, eosinophils, and plasma cells. Tumor cells express ALK with a characteristic nuclear membrane pattern, typical of this type of tumor.

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Table 1 – Clinical characteristics and evolution of the patients included in the bibliography used to support the present article and in additional articles.

Article	Age	Sex	Type of presentation	Treatment	Follow-up	Disease-free survival	Survival
Watanabe et al.[2]	70	Female	Incidental after trauma injury	Right hepatectomy	7 months	No recurrence	Living
Filips et al.[3]	32	Female	Right hypochondrium pain and fever 4 months post-partum	Segmentectomy (IVa and IVb)	1 year	No recurrence	Living
Sekaran et al.[4]	17	Female	Melenas, jaundice and abdominal pain for 18 months	Left hepatectomy	6 weeks	No recurrence	Living
Jim et al.[5]	42	Female	Fever and fatigue for 1 month	Right posterior sectionectomy	32 months	No recurrence	Living
Khalil et al.[6]	8	Male	Liver metastasis 6 months after resection o < f IMT in the right iliac fossa	Crizotinib	6 months	No recurrence	Living
Tang et al.[7]	74	Male	Fever	Segmentectomy V	Mean follow-up	No recurrence	Living
	45	Female	Fever	Segmentectomy VII	30 months	No recurrence	Living
	59	Male	Fever and Abdominal pain	Segmentectomy IV y VIII		No recurrence	Living
	53	Female	Abdominal pain	Segmentectomy V		No recurrence	Living
	45	Male	Abdominal pain	Segmentectomy VI		No recurrence	Living
Chen et al.[9]	34	Male	Weight loss and abdominal pain in the right hypochondrium	Segmentectomy V-VI	6 months	Recurrence (5 months)	Exitus
Shimodaira et al.[10]	81	Male	Pelvic IMT, treated with Miles procedure. Liver metastasis 2 months after surgery.	Surveillance	3 months	Recurrence (2 months)	Exitus
Sinha et al.	36	Female	Inflammatory mass compromising the gall bladder, liver, pylorus and first part of the duodenum	Extended cholecystectomy with resection of the pylorus and first portion of the duodenum; Billroth II reconstruction	No	No information	No information
Shang et al.	56	Female	Liver transplantation due to cirrhosis secondary to hepatitis B virus. 5 months after transplantation, she presented melena secondary to esophageal varices and a mass was detected in the *porta hepatis*; the biopsy confirmed IMT.	Conservative treatment: steroids, antibiotics, antiviral agents, immunosuppression and endoscopic ligation of varices	1 month	Recurrence (1 month)	Exitus
Raad et al.	62	Female	History of endometrial carcinoma. Follow-up imaging study detected lesion in liver segment II compatible with metastasis. The anatomopathological study after resection showed it was IMT.	Subsegmentectomy II	No	No information	No information

Table 1 (*Continued*)

Article	Age	Sex	Type of presentation	Treatment	Follow-up	Disease-free survival	Survival
Nagarajan et al.	1	Male	Hepatomegaly and anemia; mass detected in left liver lobe	Initial follow-up (suspected hamartoma); after 8 months, surgical resection due to persistent symptoms and mass	12 months	No recurrence	Living
Sürer et al.	48	Male	Pain in right hypochondrium, fever and weight loss	Surgical resection of 6-cm lesion in the right liver lobe	No	No information	Living
Berumen et al.	13	Male	Painless jaundice, asthenia; mass in hepatic hilum invading the bifurcation of both hepatic ducts, hepatic artery, portal vein, extending to the duodenum and head of pancreas.	Transhepatic biliary drainage and chemotherapy with Crizotinib; hepatotoxicity, so change to Celecoxib. After 6 months, surgery is considered, but the mass is confirmed to be unresectable. 4 months later, liver transplantation is done with pancreaticoduodenectomy.	12 months	No recurrence	Living
Thavamani et al.	10	Female	Abdominal pain and fever; 5.6-cm mass in *porta hepatis* causing secondary portal hypertension (portal thrombosis, collateral circulation, splenomegaly)	Exploratory laparotomy, biopsy with diagnosis of IMT; treatment with Meloxicam and prednisone, with reduction of tumor size in 2 years.	2 years	Disease persists after diagnosis	Living
Chablé-Montero et al.	23	Female	Right hypochondrium pain, fever; 7 cm mass in right liver lobe, suspected liver abscess	Antibiotic therapy; given the persistence of the lesion and symptoms, right hepatectomy is performed.	No	No information	No information
Schnelldorfer et al.	18	Female	Right hypochondrium pain, vomiting, weight loss; liver lesion causes left biliary dilatation.	Left lateral sectionectomy	1 year	No recurrence	Living
Solomon et al.	26	Male	Right hypochondrium pain, asthenia, weight loss	Partial left hepatectomy	No	No information	No information

Note: The series by Yang et al.[8] is not included in the table because it does not provide individual data for the patients in the original article.
Additional references to those present in the bibliography of the manuscript included in the table:
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- Nagarajan et al. JPGN 2013;57: 277–280.
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- Thavamani et al. ACG Case Rep J 2019;6:1–4.
- Chablé-Montero et al. Ann Hepatol. Sep-Oct 2012;11(5):708-9.
- Schnelldorfer et al. J Hepatobiliary Pancreat Surg (2007) 14:421–423.
- Solomon et al. Arch Pathol Lab Med (2006) 130 (10): 1548–1551.

evaluation by a multidisciplinary committee, involving left hepatectomy extended to the caudate lobe with resection of the main bile duct and the right hepatic duct up to the sectoral bifurcation, preserving the carina of both sectoral ducts. Biliary tract reconstruction was conducted with Roux-en-Y hepaticojejunostomy. The postoperative period was uneventful except for a low-output biliary fistula, which was resolved with conservative management.

The pathological anatomy report indicated the presence of a lesion measuring 2.3 × 1.9 cm with free margins, formed by a lax stroma and epithelioid cells with evident nucleoli, areas of fasciculated distribution and inflammatory infiltrate, which were compatible with inflammatory myofibroblastic tumor (IMT) (Fig. 1C). Tumor cells expressed ALK (anaplastic lymphoma kinase) (Fig. 1D). Other immunohistochemical markers related to rare neoplasms were negative, including CD34, CD21, CD117, CD23 and S100. With this information, we decided to complete follow-up without adjuvant treatment, and the patient was disease-free one year after the procedure.

IMT is a rare neoplasm that usually affects the lungs and abdominopelvic region. Although it has been related to other processes, such as inflammatory pseudotumor or plasma cell granuloma, it is recognized as a true soft tissue neoplasm of intermediate biological potential due to its ability to develop recurrence and metastasis[2]. Its appearance in the liver is rare and can lead to different forms of presentation, mimicking the behavior of other tumors. Therefore, it should be considered in the differential diagnosis of other tumors, such as hepatocarcinoma, cholangiocarcinoma, sarcomas, and benign processes like adenomas, cystic echinococcosis, or liver abscesses[2–5].

IMT has been related to infectious, inflammatory and other malignant diseases[2], although its etiology has yet to be clarified. It seems to be more common in young men[3], a fact that differentiates it from cholangiocarcinoma, in which the age of presentation is higher (except in cases of primary sclerosing cholangitis)[1]. IMT does not present clinical characteristics or specific analytical markers, and elevated acute phase reactants, such as leukocytes or C-reactive protein, are only observed in some patients. Radiologically, the suspicion arises when observing a soft tissue mass with heterogeneous enhancement that may invade neighboring structures[2,3]. When there is involvement of the extrahepatic bile duct, diagnosis is possible by ERCP and cholangioscopy[4].

As for its histology, IMT is made up of areas of proliferation of myofibroblasts mixed with collagen fibers and infiltration of inflammatory cells[2]. Macroscopically, it is usually solitary, with a firm consistency, well defined, not encapsulated and with a yellowish-white[2,3]. As a differential finding, 50%–60% of cases are positive for ALK, a factor that is related with a lower incidence of metastasis[6].

Depending on the symptoms, location and suspected diagnosis, different treatment options have been described, from surgery to conservative management. The studies by Tang[7] and Yang[8] describe the evolution of 74 patients treated surgically for hepatic IMT, all of whom were disease-free after a mean follow-up of 30 months. Yang even reported one case of tumor regression with no treatment[8]. In contrast, there also are reports of cases with only a few months of survival[9,10] related to RANBP2-ALK gene rearrangement, metastatic hepatic presentation after excision of the primary pelvic tumor, and advanced age. Resections with free margins and ALK positivity are related with a better prognosis[3]. The attached Table 1 summarizes the evolution of the patients that appear in the bibliography used.

In conclusion, whenever possible, surgical treatment seems preferable, given its intermediate biological potential. Long-term follow-up is recommended and, in case of recurrence, good response to treatment with crizotinib has been described, mainly in cases with ALK expression[6].

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