Abstract

In this report, we present the case of a 40-year-old man who was initially diagnosed with multicentric hepatocellular carcinoma (HCC), which was initially treated by hepatectomy but with tumor recurrence one year later. He then received a liver transplant from a living-related donor and, three months after the transplant, developed multiple liver lesions strongly suggestive of tumor recurrence. To our surprise, these lesions were a case of inflammatory pseudotumors that responded well to conservative treatment.

Keywords: liver transplantation, inflammatory pseudotumors, hepatocellular carcinoma

1. Introduction

Liver transplantation is one of the most important therapeutic methods used to treat hepatocellular carcinoma (HCC) (1). The discovery of new lesions after liver transplantation often leads to a broad differential diagnosis, which can only be narrowed down after a biopsy (2).

Inflammatory pseudotumors (IPTs) are rare lesions defined as masses consisting of a benign proliferation of inflammatory cells with variable degrees of fibrosis that may mimic malignancy. Pack and Baker first described these inflammatory pseudotumors (IPTL) at the hepatic level in 1953 (4). The etiology and pathogenesis of IPTL remains unknown, although infectious agents, liver trauma, vascular causes, and autoimmune diseases are assumed to be part of the etiology of IPTL (4).

The clinical manifestations of IPTL are primarily non-specific and include abdominal pain, fever, and weight loss, but quite a few cases have also been asymptomatic (5). There are some non-specific changes in laboratory tests, such as leukocytosis, anemia, or an increase in C-Reactive Protein level (CRP). Obtaining a definitive diagnostic through imaging is challenging; ultrasound, computed tomography,
and MRI, while useful, are not specific enough and can only show lesions with varying appearances or tumors that mimic HCC or a liver abscess (6).

We report a rare case of IPTL in a patient with a liver transplant for HCC, with imaging features that raised the suspicion of tumor recurrence after transplantation, which finally turned out to be IPTL that resolved with conservative treatment.

2. Case presentation

We present the case of a 40-year-old man diagnosed in 2019 with multicentric hepatocellular carcinoma (HCC) on chronic HBV hepatitis (under antiviral treatment with entecavir, 0.5 mg/day), with a history of left hepatectomy for hepatocellular carcinoma (2018) and a recurrent tumor in the right lobe of the liver. He was hospitalized for re-evaluation and to determine therapeutic management.

Laboratory tests showed normal liver function with minimal leukocytosis. CRP and fibrinogen were slightly elevated above the upper limit.

A CT scan performed in March of 2019 showed multiple nodular, hypodense lesions (Figure 1), and a native MRI showed numerous nodular lesions in the T2FS hyperintense phase, with water restriction in diffusion weighting (Figure 2), suggesting a tumoral substrate (see Figure 1).

The case was presented to the Board of Oncology and Liver Transplantation. It was decided that liver transplantation with a right HLT (hemi-liver transplantation) from a living donor (living-donor liver transplant) should be performed. Gross liver anatomy (Figure 3) presented subcapsular and intraparenchymal multiple gray-white nodular lesions (with a diameter of 0.3-0.5 cm), displaying a histopathological aspect of moderately differentiated pseudo glandular and trabecular carcinoma (Edmondson / Steiner = II/III). The adjacent liver parenchyma showed preserved architecture, as did several tumor vascular emboli (LVI+) (pT2).
After successful transplantation, immunosuppression was achieved by induction with basiliximab and maintenance with tacrolimus and mycophenolate mofetil. In addition, cytomegalovirus (CMV) prophylaxis was achieved with valganciclovir. The postoperative evolution of the graft was favorable, with improved liver function values of cholestasis, cytolysis, and liver synthesis. Serial ultrasound examinations showed the hepatic artery patent and visible (IRAH=0.66), without dilation of the biliary tree and with a permeable portal and right suprahepatic veins.

Unfortunately, three months after transplantation, laboratory tests showed a gradual increase in AFP from 9 ng/ml to 23.1 ng/ml without other significant changes in liver function tests. Tumoral markers (CEA, CA 19-9) were within normal limits. An MRI with contrast of the liver was performed with hepatocytic specificity (Eovist). A central hypointense nodule was detected during the hepato-biliary phase, with an annular peripheral uptake and restrictive character (Figure 4). These findings together could not exclude a tumoral substrate, leading to a liver biopsy to investigate the etiology of the new lesion.

The patient's case was discussed again in a multidisciplinary meeting, and it was concluded that it was either an early recurrence of HCC or inflammatory pseudotumors of the liver (IPLT). The biopsy was postponed, and antibiotic and anti-inflammatory treatment (Amoxicillin/clavulanic acid + dexamethasone for 14 days) was begun. The immunosuppressive treatment (calcineurin inhibitor) was replaced by the Mammalian Target of Rapamycin (mTOR).

A new MRI scan was performed three months after the therapeutic trial with amoxicillin/clavulanic acid and dexamethasone (Figure 5). This scan showed small signal inhomogeneities with peripheral topography and a fibrotic, retractile appearance, confirming the hypothesis of pseudo-inflammatory lesions with response to conservative treatment in the absence of a definitive histopathological examination. AFP levels also normalized. The patient was recently re-examined five years after the transplant and showed no evidence of recurrence (Figure 6).
Figure 4. Central hypointense nodular image on MRI examination with Eovist

Figure 5. MRI examination before and after the therapeutic trial – small signal inhomogeneities with peripheral topography with a retractile fibrotic appearance

Figure 6. Computed tomography was performed 5 years after transplantation, without lesions at the level of the liver graft: a) native examination, b) arterial, c) venous, and d) late examination.
3. Discussion

Liver transplantation is the treatment of choice for patients with unresectable hepatocellular carcinoma (7). Most studies estimate that tumor recurrence occurs in 8 to 20% of cases, and increasing survival rates represents another challenge for liver transplant surgeons (2). The tumor's morpho-pathology, size, and number of lesions, including the propensity for recurrence, can only be assessed by analyzing the gross specimens (8).

In the present case, the intrahepatic lesions occurred three months after transplantation for a multicentric HCC in a patient with HBV infection. The imaging raised the suspicion of tumor recurrence, with a differential diagnosis of inflammatory pseudotumors. IPTs are reactive substrates that can occur in many organs, with inflammatory pseudotumor of the liver (IPTL) being a rare and benign entity (9). IPT is a rare disease first described in the lung by Brunn in 1939 and the liver by Pack and Baker in 1953 (4).

The etiology and pathogenesis of IPT are still unknown, although an infectious agent is often involved (10). In many studies, microorganisms are the main cause (10). This hypothesis explains, in some cases, the decrease or even the disappearance of IPTs after antibiotic treatment. Other hypotheses describe autoimmune diseases like IgG4 sclerosing cholangitis and suggest administering corticosteroids (11).

Distinguishing between IPTLs and other focal liver lesions remains a challenge despite advances in radiologic imaging. Unfortunately, IPTLs can mimic malignant lesions such as lymphoma, malignant fibrous histiocytoma, hepatocellular carcinoma, metastasis, or benign lesions such as granulomas or liver abscesses (12).

In 1976, Someren classified inflammatory pseudotumors into three groups based on histology: xanthogranulomatous-type pseudotumors, plasma cell granuloma-type pseudotumors, and sclerosing pseudotumors (13). From a macroscopic point of view, IPTL can mimic a malignant tumor and appear as a single or multiple lesions, reaching 20–25 cm in size (13). In a patient with risk factors for HCC, such as chronic viral hepatitis (HBV, HCV, HBV+HDV) and liver cirrhosis, the presence of IPT may be confused with malignancy, and a correct diagnosis can only be made by biopsy or surgery (4).

A patient with IPTL may report fever, abdominal pain, and weight loss as symptoms but may also be asymptomatic. In such cases, the lesions can be identified on routine abdominal ultrasound, with possible normal liver test results. Leukocytosis, elevated C-reactive protein, and hyperfibrinogenemia may also be present (5).

Ultrasound and CT scans are nonspecific and show variable echogenicity patterns or a liver mass mimicking hepatocellular carcinoma or abscess (14). A CT scan usually shows variable lesions with contrast enhancement. IPTs may show a hypo-vascular pattern due to fibrosis, similar to metastatic liver tumors and cholangiocarcinoma (15).

MRI may show low signal intensity (hypo-intensity) on T1-weighted images with moderate to high signal intensity (hyperintensity) on the T2 sequence (16). In our case, several hypo-vascularized central nodules were detected in the hepatobiliary phase, some with annular peripheral uptake and a restrictive character in the diffusion weighting sequence.

In our case, liver biopsy was not used as a diagnostic tool because the suspected malignant lesion was assessed by imaging techniques (CT and MRI) and confirmed by the therapeutic trial. Although not used, liver biopsy plays a vital role in investigating and eventually treating liver metastases of unknown origin. This being said, there are some inherent risks with this procedure, one of them being tumor seeding via the biopsy needle, which was found in 5% of patients with hepatocellular carcinoma (HCC) who underwent percutaneous needle biopsy (17).

We found only two reported cases of IPTL after liver transplantation. Hence, a precise diagnosis of IPTL is not always easy due to the heterogeneity of this entity, as described in the literature (18). However, in the case of this patient, the lesions were multifocal, which is a more rare manifestation of IPTL than a solitary lesion. The imaging studies, the response to treatment (antibiotics and corticosteroids), and the excellent evolution throughout five years
strongly suggest that this patient had a case of pseudo-inflammatory liver tumors. It has only been described in the literature in two cases following liver transplantation, but in neither case did the patient have hepatocellular carcinoma before transplantation, making this case truly unique and captivating.

4. Conclusion

In summary, we present a case of multiple IPT of a transplanted liver that regressed under antibiotic and corticosteroid treatment. This is the first case of inflammatory pseudotumors of the post-transplant liver in a patient with a history of hepatocellular carcinoma described in the literature.

Abbreviations
ADC – Apparent diffusion coefficient
CRP – C-reactive protein
CT – computed tomography
DWI – diffusion-weighted imaging
EBV – Epstein-Barr Virus
HB – hepatobiliary
HBV – hepatitis B virus
HCV – hepatitis C virus
HDV – hepatitis D virus
HCC – hepatocellular carcinoma
HIV – human immunodeficiency virus
IPT – Inflammatory pseudotumor
IPTL – Inflammatory pseudotumor of the liver
MRI – Magnetic resonance imaging
mTOR – Mammalian Target of Rapamycin
T2FS – T2 Fat-saturation

Statements
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