Hepatic loss in a young patient: a very ‘cold case’

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Case presentation

Dr. De Francesco. A 28-year-old male farmer, complaining of mild, recurrent right upper quadrant and chest pain was referred to gastroenterology. The patient had received sporadic and unsuccessful NSAID-based therapy during the prior 2 years. Bowel movements were regular and no fever was present. He smoked ten cigarettes daily. Physical examination was unrewarding, but abdomen palpation revealed exacerbation of tenderness in the liver area with modest hepatomegaly. An abdominal ultrasonography was performed showing a round mass, 8 cm in diameter, localized in the right hepatic lobe, with a heterogeneous ultrasound signal in the central area. Laboratory tests found elevated levels of alanine aminotransferase ($\times 1.5$ normal value), alkaline phosphatase and γ -glutamyltranspeptidase (both $\times 1.3$ normal value) and increased values of erythro-sedimentation rate (48 mm/h), C-reactive protein ($\times 5.5$ normal value), cholesterol level ($\times 1.2$ normal value) and triglycerides level ($\times 2$ normal value); all other biochemical

tests, including α -fetoprotein, were in the normal range. Computed tomography (CT scan) confirmed the presence of a round mass (11×10 cm) in the right hepatic lobe, compressing the right hepatic vein. The lesion appeared heterogeneous and hypodense, with a peripheral enhancement in the arterial phase and low enhancement in the portal and delayed phase. A pseudo-capsule was evident with a small interruption in the proximity of a satellite nodule of 1 cm (Fig. 1).

Differential diagnosis

Prof Ierardi, Dr. Zullo and Dr. Hassan. When interpreting a liver lesion detected by an imaging study—such as at ultrasound—the contextual evaluation of the remaining parenchyma is crucial. In detail, a mass with onset in a liver with cirrhosis, specifically when >2 cm in diameter, should be interpreted as a focal hepatocellular carcinoma (HCC) until proven otherwise. Generally, HCC presents as hypo–hyper echoic lesion on ultrasound, with hypervascularization and arterovenous shunts at CT-angiography. Evidence of bile duct dilatation evokes the presence of a cholangiocarcinoma. α -fetoprotein (AFP) is the tumor marker of choice for HCC confirmation, and values >400 ng/mL are highly indicative of disease. Nevertheless, 30% of patients with HCC <2 cm have normal AFP levels, 20% of HCC produce no AFP, and levels from 20 to 250 are frequently observed in benign regenerating nodules or viral cirrhosis.

On the other hand, a hepatic loss encountered in a normal-appearing liver parenchyma is generally a benign lesion. Hemangioma (diameter range: 1–10 cm; hyper-echoic at ultrasound, without arterovenous shunts and with persistent enhancement on CT scan), adenoma (diameter:

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Fig. 1 Computed tomography image: round mass (11 × 10 cm) in the right hepatic lobe, centrally heterogeneous and constantly hypodense. A pseudo-capsule is evident with small interruption in the proximity of a satellite nodule of 1 cm

1–10 cm, hyperechoic, with internal necrotic areas, hypervascularized) and focal nodular hyperplasia (diameter <3 cm, hypo-isoechoic with a central arterial signal, hypervascularized) are the most frequent lesions reported to occur in up to 20% of the general population [1]. A pyogenic hepatic abscess can be suspected in the presence of fever, granulocytic leucocytosis and systemic sign of sepsis. Distinctive ultrasound, CT scan images and highly specific serological tests are indicative of amebic hepatic abscess (ultrasound: hypoechoic lesion, with internal necrotic areas; CT scan: heterogeneous lesion without enhancement after contrast medium) and hepatic hydatidosis (ultrasound: anechoic round lesion with internal punctiform frame-like calcifications; CT scan: hypodense lesion, with internal peripheral calcifications without enhancement after contrast medium) [2, 3].

Further investigation

Dr. De Francesco and Dr. Zullo. Before surgery, all potential causes were investigated. The patient denied alcohol abuse and exposure to toxic agents such as fertilizers or herbicides. He was not taking any drugs or herbal medications. HBV, HCV, CMV, herpes virus and Epstein–Barr virus, as well as antinuclear, antimitochondrial and anti-LKM autoantibodies, and specific antibodies for *E. granulosus* and *E. histolytica* were not detectable. Normal values of α 1-antitrypsin, plasmatic protoporphyrins, cupremia, ceruloplasmin and copper urinary excretion were found. Normal levels of sexual hormones and a normal male karyotype were demonstrated. A heterozygosis

status for the mutated H63D gene was found. However, hemochromatosis was ruled out based on normal values of both ferritinemia (370 ng/ml, normal range: 225–380) and transferrin saturation levels (27%). Both upper endoscopy and colonoscopy were negative.

Surgical treatment and histological diagnosis

Dr. Cianci, Dr. Corsi, Dr. D’Agnessa and Dr. Castriota.

Partial resection of the right hepatic lobe was performed. The resected specimen appeared as a single and well-demarcated yellowish, round mass of 10 cm in diameter, with necrotic and hemorrhagic internal areas. A pseudo-capsule was evident with small interruption in the proximity of a satellite nodule of 1 cm (Fig. 2). The surrounding hepatic parenchyma and the remaining left lobe did not show any signs of fibrotic or cirrhotic evolution. Histological assessment found an HCC. The neoplastic cells were arranged in solid sheets, with loss of typical lobular architecture, showing moderate nuclear pleomorphism and prominent nucleoli (Edmondson–Steiner grade II) (Fig. 3). Left lobe hepatic parenchyma showed chronic active hepatitis with inflammatory infiltration of the portal district and diffusion into the lobular zone and piecemeal necrosis without evidences of steatosis or steatohepatitis. Biliary duct epithelium impairment was clearly distinguished (Fig. 4). Histological assessment with Pearls specific staining excluded iron accumulation in the liver.

Fig. 2 Resected specimen: well-demarcated, round mass of 10 cm in diameter, yellowish, with necrotic and hemorrhagic internal areas after partial resection of the right hepatic lobe. A pseudo-capsule is evident with small interruption in the proximity of a satellite nodule of 1 cm

Fig. 3 Microscopic features of the hepatocellular carcinoma (hematoxylin and eosin staining). The neoplastic cells are arranged in solid sheets, with loss of typical lobular architecture, and show moderate nuclear pleomorphism and prominent nucleoli (Edmondson-Steiner grade II)

Follow-up

Dr. Stoppino. 6 months following surgery, the patient was asymptomatic. Abdominal ultrasonography found no evidence of HCC recurrences in remaining and regenerating liver. Normal serum levels of α -fetoprotein were confirmed.

Discussion

Dr. De Francesco and Dr. Zullo. The present case of HCC shows some unusual characteristics. HCC carcinoma appears as a frequent complication of liver cirrhosis, through a slow carcinogenetic process. Indeed, the peak of HCC incidence occurs in the fifth and sixth decades of life, with a mean age of 65 years at the time of diagnosis [4]. None of these characteristics were present in our case. Viral infections and metabolic disorders typically associated with both cirrhosis and HCC, such as hemochromatosis and

Fig. 4 Chronic active hepatitis. Inflammatory infiltration of the portal district with diffusion into the lobular zone, piecemeal necrosis and biliary duct epithelium impairment may be distinguished

Wilson's disease, porphyria and α 1-antitrypsin deficiency were excluded [4–6]. Similarly, more common diseases such as non-alcoholic fatty liver disease (NAFLD), diabetes and obesity, more recently associated as risk factors for HCC [7, 8], were ruled out. The role of anabolic-androgenic steroid abuse and endocrine disorders in the progression of “adenoma to carcinoma” [9–11] could not be invoked in our patient. Finally, the potential involvement of a rare constitutional chromosomal aberration was not supported by a normal karyotype assessment [12, 13].

The sole potential disorder we found was a heterozygosis status for a mutated H63D gene that was involved in hemochromatosis. A distinctly increased risk (150–200 times) of HCC is present in haemochromatosis when cirrhosis develops, [6] and some cases of HCC in patients without liver cirrhosis have also been reported [14, 15]. However, hemochromatosis was ruled out based on normal values of ferritinemia and transferrin saturation levels, and absence of iron accumulation in the liver.

Therefore, in our patient, a large mass of HCC surprisingly occurred in young age on liver with cryptogenic active hepatitis without cirrhotic evolution. In addition,

normal α -fetoprotein levels were observed, despite the large tumor diameter.

The unsolved question remains as far as the clinical prognosis is concerned, due to the histological features of chronic active hepatitis without any recognized cause. Indeed, such a cryptogenic hepatitis prevents any specific therapeutic approach, and both evolution into cirrhosis as well as HCC recurrence is possible, particularly when considering the young age of the patient. We therefore consider such a patient as a very ‘cold case’; a strict follow-up represents the only possible strategy.

Conflict of interest None.

References

1. Assy N, Nasser G, Djibre A, Beniashvili Z, Elias S, Zidan J (2009) Characteristics of common solid liver lesions and recommendations for diagnostic workup. *World J Gastroenterol* 15:3217–3227
2. Martinez-Palomo A. (1992) Amoebiasis, giardiasis and cryptosporidiosis. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J. *Oxford textbook of clinical hepatology*. Oxford Medical Publication, pp 696–701
3. Miguet JP, Bresson-Hadny S, Vuitton D. (1992) Echinococcosis of the liver. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J. *Oxford textbook of clinical hepatology*. Oxford Medical Publication, pp 721–730
4. El-Serag HB (2004) Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology* 127:S27–S34
5. Blonski W, Kotlyar DS, Forde KA (2010) Non-viral causes of hepatocellular carcinoma. *World J Gastroenterol* 16:3603–3615
6. Fargion S, Fracanzani AL, Piperno A et al (1994) Prognostic factors for hepatocellular carcinoma in genetic hemochromatosis. *Hepatology* 20:1426–1431
7. Davila JA, Morgan RO, Shaib Y et al (2005) Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 54:533–539
8. Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok A (2002) NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 36:1349–1354
9. Gyorffy EJ, Bredfeldt JE, Black WC (1989) Transformation of hepatic cell adenoma to hepatocellular carcinoma due to oral contraceptive use. *Ann Intern Med* 110:489–490
10. Closset J, Veys I, Peny MO et al (2000) Retrospective analysis of 29 patients surgically treated for hepatocellular adenoma or focal nodular hyperplasia. *Hepatogastroenterology* 47:1382–1384
11. Giannitrapani L, Soresi M, La Spada E, Cervello M, D'Alessandro N, Montalto G (2006) Sex hormones and risk of liver tumor. *Ann NY Acad Sci* 1089:228–236
12. Bardi G, Johansson B, Pandis N et al (1992) Trisomy 2 as the sole chromosomal abnormality in a hepatoblastoma. *Genes Chromosome Canc* 4:78–80
13. Ruijs MW, van Andel RN, Oshima J, Madan K, Nieuwint AW, Aalfs CM (2003) Atypical progeroid syndrome: an unknown helicase gene defect? *Am J Med Genet A* 116:295–299
14. Tomao S, Romiti A, Mozzicafreddo A, Raffaele M, Zullo A, Intonaci A (1998) Onset of hepatocellular carcinoma in a non-cirrhotic patient affected with haemochromatosis. *Oncol Rep* 5:723–725
15. Fellows W, Stewart M, Jeffcoate WJ et al (1988) Hepatocellular carcinoma in primary hemochromatosis in the absence of cirrhosis. *Gut* 29:1603–1606