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Malignant transformation of hepatocellular adenoma

To the Editor:

We read with interest the paper by Chopinet *et al.* on long-term outcomes following resection of hepatocellular adenoma with malignant transformation (MT-HCA).[1]

In their retrospective surgical study, resected specimens were divided into 2 groups: HCA with small foci of malignancy <1 cm (SF-HCA, 23 patients) and malignant HCA with macroscopic malignant nodules larger than 1 cm (M-HCA, 17 patients). Recurrence free-survival (RFS) after liver resection (LR) for MT-HCA was compared to patients resected for hepatocellular carcinoma (HCC) occurring on normal liver parenchyma (NP-HCC). Of these MT-HCA,16/40 (40%) had β-catenin mutations, 19/40 (47.5%) were inflammatory, 1 was *HNF1A*-mutated and 4 (10%) were unclassified HCA. Microvascular invasion (12% *vs.* 0%) and satellite nodules (25% *vs.* 4%) were more frequently observed in M-HCA than in SF-HCA. After a median follow-up of 67 months, 10 (25%) patients with MT-HCA had tumor recurrence, including 9 with M-HCA and 1 with SF-HCA. M-HCA was linked to significantly poorer RFS rates than SF-HCA. The authors identified age >55 years, presence of satellite nodes, and microvascular invasion as risk factors for long-term recurrence. This study has the major merit of being the only one available on long-term risk of recurrence in patients with MT-HCA following LR, compared to NP-HCC. However, as mentioned by the authors, this study has major bias.

i) The definitions of SF-HCA and MT-HCA were determined on operative specimens and defined by the extent of the malignant foci area. They ignore the number of foci, the size and number of malignant nodules; the notion of borderline lesions was not considered. Defining inflammatory HCA (IHCA) based on serum amyloid A positivity in at least 10% of tumorous hepatocytes will inevitably lead to the overestimation of its prevalence; shHCA were not classified.
ii) The long study period between 2001-2019 is incompatible with the progress made on MRI, HCA classification, molecular analysis.
iii) The low number of patients included (40 MT-HCA, and 40 NP-HCC) prevents any solid conclusion from being drawn.

This led us to review our own experience. Our HCA database includes 250 cases (33 men). All cases with the terms HCC and borderline lesions were retrieved. It includes only cases with obvious pathological proof that HCC was developed on HCA. These patients were regularly followed. Pathological (macroscopy and microcopy), surgical and clinical records were reviewed, as well as slides (H&E, reticulin, CD34, MIB1, immunomarkers for HCA classification.[2]) Data on deaths related or not to HCC were collected as was follow-up data for patients alive without recurrence. Data are summarized in Table S1.

i) Contrary to Chopinet *et al.*, we did not observe HCC in patients with IHCA, which is surprisingly the major subtype in Chopinet *et al.*'s paper. It is known that HCC, without any previous HCA, can frequently overexpress inflammatory proteins[3] and exhibit low levels of LFABP,[4] that can be misleading with the diagnosis of MT-HCA. The majority of our cases with malignant features were HCAs with a high level of β-catenin pathway activation (mainly due to exon 3 non S45 mutation or large deletion).
ii) In our series, we observed a limited number of HCC (12 cases; 4.8%) and borderline HCA/HCC (17 cases; 6.8%). One could argue that our definition of borderline lesion could correspond to SF-HCA described by Chopinet *et al.* or identified by others as very well-differentiated HCC[5] or HUMP.[6]
iii) In the majority of our MT-HCA, 20 to 80% of the tumoral volume were well differentiated with no microvascular invasion or satellite nodules.
iv) Recurrence and death was explained in 2 cases by voluminous HCC compared to the total volume of the tumor (poorly differentiated HCC in one case), and by the lack of effective surgery in 2 cases. The fifth death was not related to HCC.

Data on long-term outcomes are important for the development of optimal management strategies for HCA, especially since derivation of NP-HCC from an HCA remains a challenge.[7–10] Today, sex and size of HCA remain the most well-established parameters to guide treatment decisions. Elective liver resection is recommended in all men, while women are subjected to surgery when HCA diameter is greater than 5 cm and/or size has been progressing despite life-style changes. Nonetheless, multiple case reports showed malignant transformation in HCAs with diameters <5 cm, while other studies suggest an elective surgery for diameters >4 or >8 cm, opening a debate around the optimal cut-off values for surgical treatment. Selected patients obviously benefit from conservative therapy, such as the cessation of exogenous hormone intake.

The understanding of HCA risk factors has evolved gradually to include: demographic factors (age, sex,) environmental factors (oral contraception, drugs, anabolic steroids, obesity, metabolic syndrome, alcohol); underlying liver disease (non-alcoholic steatohepatitis, vascular liver diseases and even alcohol-related cirrhosis), genetic diseases (MODY3, glycogenosis, familial adenomatous polyposis…) and molecular characteristics. The time has come to individually assess the risk of hepatocarcinogenesis for each patient with HCA in order to provide risk-adjusted management and treatment. This can only be done at a European/international level.

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References
[1] Chopinet S, Cauchy F, Hobeika C, Beaufrère A, Poté N, Farges O, et al. Long-term outcomes following resection of hepatocellular adenomas with small foci of malignant transformation or malignant adenomas. JHEP Rep 2021;3:100326.
[2] Bioulac-Sage P, Gouw ASH, Balabaud C, Sempoux C. Hepatocellular adenoma: what we know, what we do not know, and why it matters. Histopathology. PMID: 34856012. https://doi.org/10.1111/his.14605 (under revision).
[3] Shin JH, Kim CJ, Jeon EJ, Sung CO, Shin HJ, YU JCE. Overexpression of C-reactive protein as a poor prognostic marker of resectable hepatocellular carcinomas. J Pathol Transl Med 2015;49:105–111.
[4] Cho SJ, Ferrell LD, Gill RM. Expression of liver fatty acid binding protein in hepatocellular carcinoma? Mod Pathol 2021;33:665–675.
[5] Kakar S, Grenert JP, Paradis V, Pote N, Jakate S, Ferrell LD. Hepatocellular carcinoma arising in adenoma: similar immunohistochemical and cytogenetic features in adenoma and hepatocellular carcinoma portions of the tumor. Mod Pathol 2014;27:1499–1509.
[6] Balabaud C, Bioulac-Sage P, Ferrell L, Kakar S, Paradis V, Quaglia A, et al. Well-differentiated hepatocellular neoplasm of uncertain malignant potential. Hum Pathol 2015;46:634–635.
[7] Stoot JH, Coelen RJ, De Jong MC, Dejong CH. Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. HPB (Oxford) 2010;12:509–522.
[8] Sempoux C, Balabaud C, Bioulac-Sage P. Malignant transformation of hepatocellular adenoma. Hepat Oncol 2014;1:421–431.
[9] Liu TC, Vachharajani N, Chapman WC, Brunt EM. Noncirrhotic hepatocellular carcinoma: derivation from hepatocellular adenoma? Clinicopathologic analysis. Mod Pathol 2014;27:420–432.
[10] Thevathasan T, Colbatzky T, Schmelzle M, Pratschke J, Krenzien F. Risk factors for malignant transformation of hepatocellular adenoma to hepatocellular carcinoma: protocol for systematic review and meta-analysis. BMJ Open 2021;11:e045733.

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