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Phenotype or Genotype: Decision-Making Dilemmas in Hepatocellular Adenoma

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Hepatocellular adenomas (HCA) may undergo malignant transformation to hepatocellular carcinoma (HCC). Several HCA subtypes can be distinguished: H-HCA (characterized by biallelic inactivating mutation of hepatocyte nuclear factor 1A), I-HCA (activating mutations in different oncogenes of the Janus kinase [JAK]/signal transducer and activator of transcription [STAT] pathway), B-HCA (mutation in the catenin beta 1 [CTNNB1] gene encoding for β-catenin protein, which can be situated on exon 3, 7, or 8), B-IHCA (shares both JAK/STAT pathway activation and CTNNB1 mutation) and sh-HCA (activation of sonic hedgehog signaling pathway).[1,2] In cases of multiple lesions, different subtypes of HCA may be observed.[1,3] B-(I)HCA are associated with a higher risk of malignant transformation. It has been described that especially B-(I)HCA with exon 3 mutations (B^{ex3}(I)HCA) are at high risk of HCC development, whereas the risk in those with exon 7/8 mutations ($B^{ex7,8}$(I)HCA) appears to be low.[2,4] In this report, we present 2 patients with HCA and unusual pathological findings that might impact clinical views.

Case 1

A 40-year-old female patient underwent a segmentectomy because of an inhomogeneous hepatic mass. Macroscopic examination showed a solid 90-mm lesion with light and dark brown areas and some small (1-14 mm) whitish nodules (Fig. 1A). Microscopic examination showed a hepatocellular proliferation without atypical features at the background (Fig. 1B,C). Glutamine synthetase (GS) appreciated a faint heterogeneous expression at the center and a reinforcement at the periphery, a surrogate pattern of β-catenin activation. C-reactive protein (CRP) staining was negative (Fig. 1D). The sections corresponding to the whitish nodules revealed decreased and disorganized reticulin network and positivity for glypican-3 (Fig. 1E), features pointing toward HCC transformation with good differentiation. Additional molecular analysis of the main lesion confirmed exon 7 mutation in CTNNB1 (B^{ex7}HCA) and telomerase reverse-transcriptase (TERT) promoter mutation in the areas with HCC transformation.

In a benchmark study from 2017, <4% of included patients with HCA had B^{ex7}HCA, and malignant transformation was observed in none of the patients with $B^{ex7,8}$HCA.[2] The present case shows that although the risk of malignant transformation in B^{ex7}HCA is lower compared with B^{ex3}HCA, it should not be neglected.

Case 2

A 32-year-old woman underwent a segmentectomy because of multiple liver lesions. Macroscopic examination showed two well-demarcated, nonencapsulated lesions of 65 and 13 mm (Fig. 2A-I,B-I).

Abbreviations: CRP, C-reactive protein; CTNNB1, catenin beta 1; GS, glutamine synthetase; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma.

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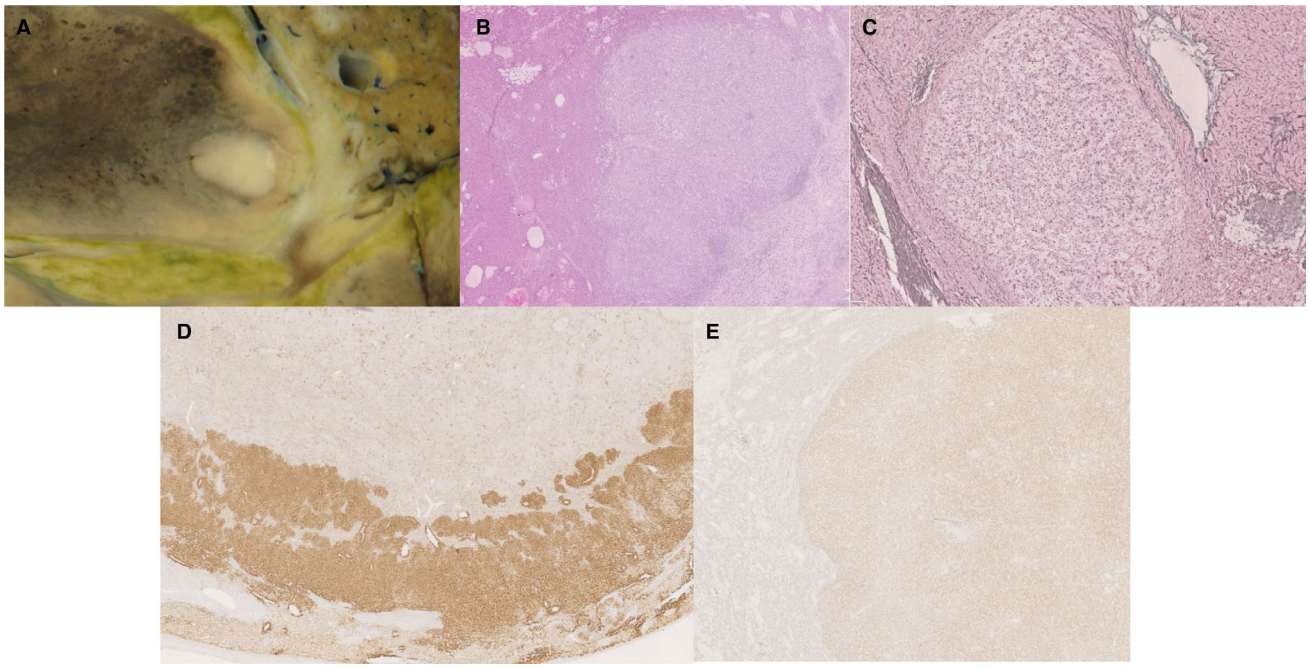

FIG. 1. Macroscopic and microscopic images, Case 1: (A) macroscopy of one of the small whitish nodules in the hemorrhagic background of the HCA, (B) microscopy of hematoxylin and eosin staining, (C) microscopy of reticulin staining denoting the disorganized reticulin with forming of broad liver plates, (D) immunohistochemistry of CRP with dense reinforcement of expression at the periphery, (E) immunohistochemistry of diffuse positive glypican-3 staining.

Both had alternating pale areas with dark red foci. Microscopic examination showed features of I-HCA with sinusoidal dilatation and inflammatory infiltrates in the pseudoportal areas (Fig. 2A-II,B-II). Immunohistochemistry demonstrated a dense and diffuse staining for CRP (Fig. 2A-III,B-III). Moreover, in the small nodule, a diffuse staining was found for GS with a more intense staining at the periphery of the lesion, suggesting β-catenin activation (Fig. 2A-IV). Molecular analysis of the small nodule confirmed CTNNB1 mutation in exon 3. The large nodule was negative for CTNNB1 mutation.

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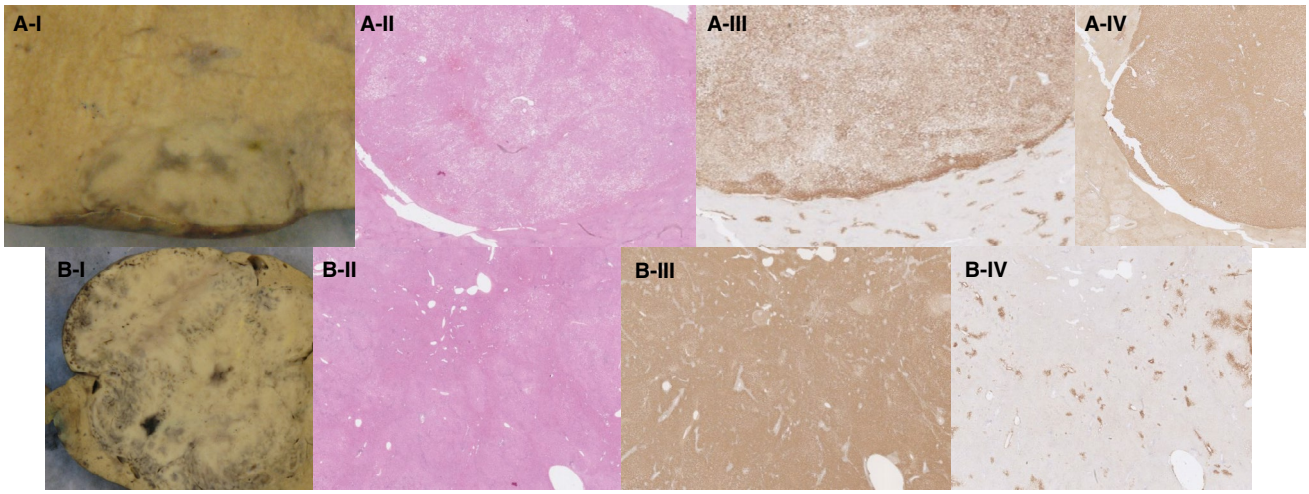

FIG. 2. Macroscopic and microscopic images, Case 2: (A) macroscopic and microscopic images of the small lesion, (A-I) macroscopy, (A-II) microscopy of hematoxylin and eosin (H-E) staining, (A-III) immunohistochemistry of CRP with diffuse positive staining, (A-IV) immunohistochemistry of GS with diffuse positive staining; (B) macroscopic and microscopic images of the large lesion, (B-I) macroscopy, (B-II) microscopy of H-E staining, (B-III) immunohistochemistry of CRP with diffuse positive staining, and (B-IV) immunohistochemistry of GS with perivascular staining, no diffuse pattern.

Guidelines on benign liver tumors advise to base management decisions in patients with multiple HCA on the largest lesion.[5] The aforementioned benchmark article describes intertumor heterogeneity with at least one B^{ex3}(I)HCA in 9 patients with multiple HCA.[2] Only 1 patient was described in whom the largest was an H-HCA and a smaller B^{ex3}HCA; in the remaining patients, the largest tumor had the CTNNB1 mutation.

In conclusion, these cases illustrate the existent risk of malignant transformation in $B^{ex7/8}$HCA. Pending defined indications for molecular analysis, we would propose performing mutational examination in all cases with inconclusive/equivocal immunohistochemistry, at least on biopsy material. Prospectively, this will lead to data collection and better understanding of the oncogenic β-catenin exon 7/8 and TERT mutations. Secondly, in the management of multiple HCA, the final decision should be made based on pathomolecular subclassification along with the diameter.

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