**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). In cases of multiple lesions, different subtypes of HCA may be observed. 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\textsuperscript{ex3}(I)HCA) are at high risk of HCC development, whereas the risk in those with exon 7/8 mutations (B\textsuperscript{ex7,8}(I)HCA) appears to be low. 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\textsuperscript{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\textsuperscript{ex7}HCA, and malignant transformation was observed in none of the patients with B\textsuperscript{ex7,8}HCA. The present case shows that although the risk of malignant transformation in B\textsuperscript{ex7}HCA is lower compared with B\textsuperscript{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, noncapsulated lesions of 65 and 13 mm (Fig. 2A–I, B–I).
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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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 \(\beta\)-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.

**REFERENCES**


