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MINI REVIEW

Snapshot summary of diagnosis and management of hepatocellular adenoma subtypes

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KEYWORDS
Hepatocellular adenoma;
Immunohistochemical classification;
Overview

Abstract Hepatocellular adenomas (HCA) are rare benign hepatocellular tumors occurring mainly in women taking oral contraceptives with 2 major complications: severe bleeding and malignant transformation that can be avoided if nodules exceeding 5 cm are resected. This simple attitude has been challenged in the recent years with HCA in men, in young adolescent, in aged persons, and complications in hepatocellular adenomas below 5 cm. The discovery of specific mutations leading to specific phenotypes has modified the clinical spectrum of the disease. The phenotypic immune classification of HCA based on the molecular classification is being widely used in liver referral centers. The aim of this snapshot is to briefly present for each subtype the clinical, pathological, immuno-pathological criteria as well as the risk of complications and guidelines for treatment and management.

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Tables 1—4

Table 1 Hepatocellular adenoma. Overview.

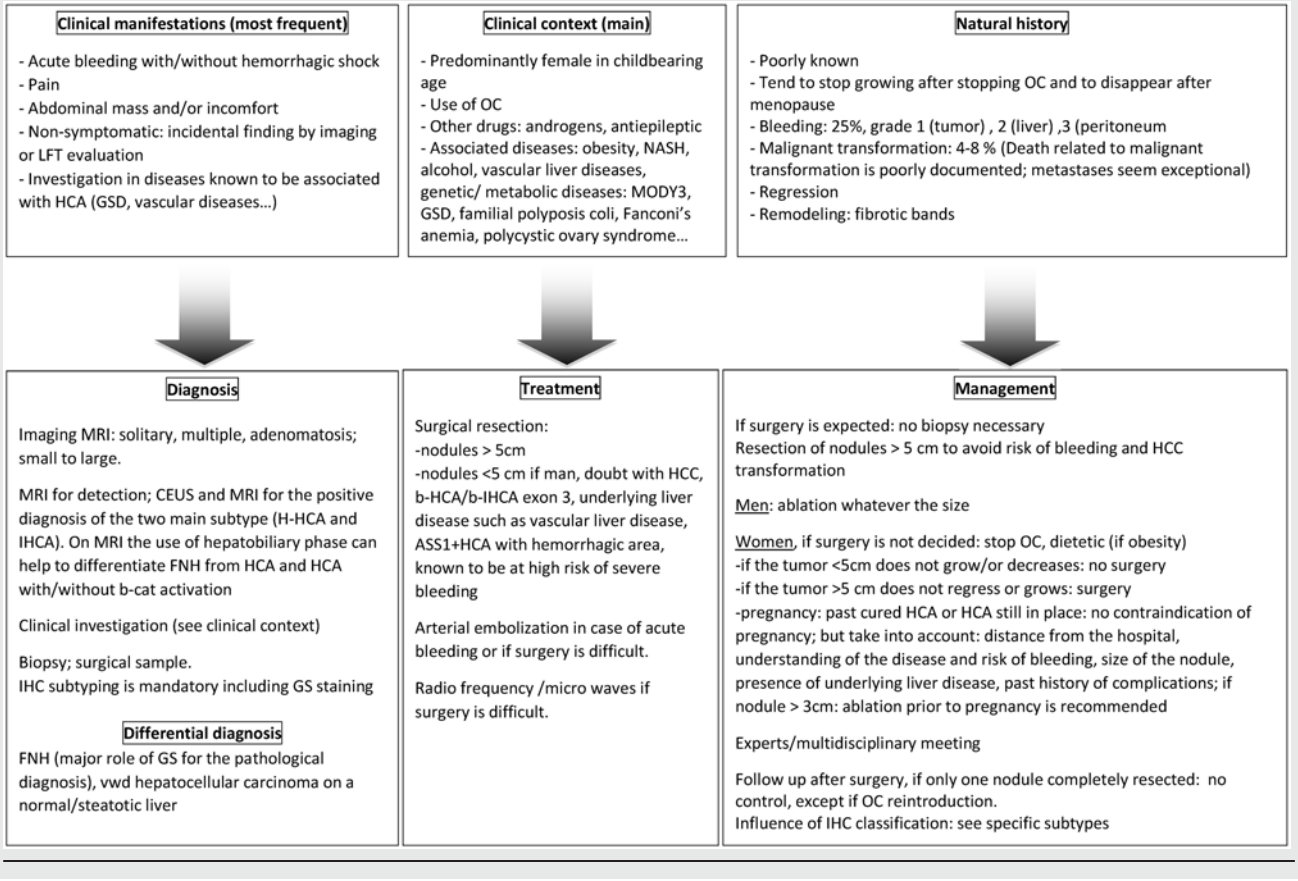

Table 2 Hepatocellular adenoma specificity according to subtypes: Bordeaux immuno-classification (1) — Fig 1.

H-HCA 30% (Figure 2)

- ***Imaging*:** solitary, multiple, adenomatosis

MRI specific criteria:
Typical pattern*: (1) diffuse and homogeneous signal drop out on T1-weighted chemical shift sequence due to steatosis, (2) iso or slightly hyper signal on T2 weighted images, (3) weak or moderate enhancement in the arterial phase, with no persistent enhancement in the portal venous and delayed phases. *Biopsy not mandatory
Atypical patterns*: *Biopsy necessary for diagnosis

- ***Pathology***

Typical pattern: macro/micro steatosis, ballooning, clear cells except along vascular axis (whatever the size of nodules, even micro H-HCA)
Atypical patterns: no or little steatosis, often associated with myxoid areas, pseudo-glands, decreased reticulin, focally abnormal GS, lipofuschins

- ***IHC*:** LFABP totally absent.
- ***Molecular biology*:** not necessary for routine
- ***Differential diagnosis:*** vwd HCC if atypical pattern, ASS1+HCA (since LFABP often decreased)
- **Specific etiology:** MODY 3 patient or family context (blood tests)
- ***Management*:** surveillance; US is not necessary once a solitary nodule has been removed, even if small H-HCA exist outside the resected lesion area

Rule of 5 cm can be overcome if diagnosis is certain

IHCA 32% (Figure 3)

- ***Imaging*:** solitary, multiple, adenomatosis (less frequent)

MRI specific criteria:
Typical pattern: (1) Marked hyper signal on T2W sequences diffuse or predominant in the outer part of the lesion (atoll sign), (2) strong arterial enhancement, (3) with persistent enhancement in portal venous or delayed phase, diffuse, or in the peripheral rim (atoll sign).
NTL is steatotic in 30% of cases
Obesity
Atypical patterns*: Biopsy necessary for diagnosis and also to rule out association of b-catenin activation (see b-IHCA)

- ***Pathology***

Typical: sinusoidal dilatation, congestion, pseudo portal tracts with thick wall arteries, inflammation, ductular reaction
Atypical: lack of one or several typical criteria

- ***IHC***: CRP + in T/ absent in NTL. GS staining is by definition not abnormally expressed, present only around some veins mainly at the periphery. An abnormal staining may indicate b-IHCA.

CRP can be positive in NTL usually to lesser extent/ intensity, i.e in case of major hemorrhage

- ***Molecular biology*:** not necessary for routine diagnosis
- ***Management*:** stopping OC

Time of discovery and time expected for menopause is crucial to take decision of ablation
The only fear in multiple IHCA is the possibility that one of the nodule is b-IHCA . Surveillance to detect any growth.

ASS1+HCA 10%° (Figure 4)

- ***-Imaging*:** solitary to multiple

MRI criteria: often large necrotic and/or hemorrhagic areas, remodeling; presence of peculiar "fluid" vacuoles
Frequent obesity (morbid)
Biopsy to be discussed with caution, due to possible bleeding risk, even for tumors <5cm

- ***Pathology***

Typical: quite homogeneous mass; bland pattern with more or less numerous vacuoles filled with blood or degradated products, many small arteries, some fibrotic bands (remodeling), some sinusoidal dilatation areas +/- large hemorrhagic areas
NTL often highly steatotic
Atypical: lack of one or several major criteria

- ***IHC***: LFABP + (but often decreased), CRP -, GS - ASS1+ in T > NTL
- ***Molecular biology*:** not necessary for routine diagnosis
- ***Management*:** risk of bleeding even for small nodules; hemorrhagic shock. Pregnancy: If the diagnosis is established with a focal hemorrhagic area, surgery should be discussed even for small lesions.

°similar if not identical to shHCA potentially identified by PTGDS IHC; further studies are needed to characterize these subtypes

Table 3 Hepatocellular adenoma specificity according to subtypes: Bordeaux immuno-classification (2) — Fig 1.

b HCA / b IHCA	• **b-cat activation is not yet related to specific imaging profiles** (see imaging table 1) • It is important to **distinguish b-HCA from b-IHCA**; it is mandatory to perform CRP and GS. -b-HCA a single molecular/IHC abnormality: b-cat pathway activation (GS+), CRP - -b-IHCA: 2 molecular/IHC abnormalities: inflammatory and b-cat pathways activation (CRP +, GS +), the second one occurring probably as a secondary event To evaluate the risk of malignant transformation, it is important in both groups to recognize ex 3 (high risk) from ex 7/8 mutations (low/no risk) and to differentiate ex 3 non-S45 from S45 • **Management: depends on b-cat mutation (biopsy is presently mandatory).** -b-HCA and b-IHCA ex 3 non S45 should be resected. b-HCA and b-IHCA ex 3 S45 resection should be considered if there are cytological/architectural abnormalities. -b-HCA and b-IHCA ex 7/8 in the absence of cytological abnormalities can be followed.	
b-HCA		**b-IHCA**
Exon 3 (non S45) (Figure not shown) A cause can be found (inconstant): male hormone administration Vascular liver diseases	-GS diffuse /strong; aberrant b-cat nuclear staining: from many to few nuclei: confirmation of b-cat mutation by molecular analysis is not necessary for routine diagnosis. -H&E: from normal to borderline lesion (cellular atypia, pseudo glands) to HCC foci -loss of reticulin, CD 34 usually not diffuse (except in HCC foci) -risk of malignant transformation. TERT mutation analysis is promising	**Exon 3 (non S45)** (Figure not shown) If several nodules, some may be IHCA and others b-IHCA. It is important to identify those b-IHCA ex 3
Exon 3 S45 CD34 diffusely positive except at the border	GS "starry sky" pattern: from many to few stars GS + border: usually thin irregular, rather compact	**Exon 3 S45:** as above if several nodules Occasional GS packs around/beyond HV CD 34 expended but not diffusely positive **(Figure 5)**
Exon 7/8 (Figure not shown) CD 34 diffusely positive except at the border Distinction between S45 and 7/8 may be difficult	GS: usually faint or not at all in the middle of HCA GS + border: usually thick, irregular, occasionally in two or more layers	**Exon 7/8** (Figure not shown) Occasional GS packs around/beyond HV CD34 rarely diffuse Distinction may be difficult between b-IHCA 7/8 and S45 as well as with IHCA

Table 4 Hepatocellular adenoma specificity according to subtypes: Bordeaux immuno-classification (3) — Fig 1.

UHCA

They correspond to 3 entities (<5%)
-True UHCA: all HCA markers negative
- HCA that cannot be classified by IHC or molecular analysis (i.e. HCA with some GS abnormalities but no b-cat mutation found)
- HCA almost entirely hemorrhagic/necrotic (no sufficient viable tissue)

Difficult cases

- HCA in GSD: various HCA subtypes, HCA versus FNH in case of remodelling with fibrous bands
- HCA versus vwdHCC, in case of some cytological/architectural atypia
- HCA massive form, involving near the whole liver

Place of molecular biology

MB is gold standard , possible on paraffin sections for b-cat

Other considerations

-Will HCA disappear? probably not: OC (consumption is decreasing); obesity, NASH
-In addition: male hormones intake (body builders); HCA discovered outside the context of normal healthy liver (i.e. alcoholic cirrhosis, vascular liver diseases)
-Association of HCA of different subtypes in a same liver; HCA and FNH
-Pregnancy: a real clinical issue due to the risk of bleeding; not anymore a contra indication, but needs a strict follow up (see table 1)
- Acute bleeding and malignant transformation: major clinical issue
- Natural history: need for a registry
- Liver center (one or several according the size of the country: multidisciplinary approach: hepatologists, liver pathologists, liver radiologists, liver surgeons)
- Patient's information : necessity of a blog
-Worldwide distribution of HCA is unknown.

The future of HCA classification based on genomic and proteomic analysis

- Baum (1973) links OC to the occurrence of HCA, number of publications increased with the immuno- classification.
-The clinical relevance of the classification is not clearly understood; its main success is linked to the possibility to differentiate HCA from FNH, and to better propose a rational management.
- Progress in the identification of HCA subtypes by radiologists.
- Remain two major issues: differential diagnosis between HCA borderline from a vwd HCC, identification of HCA (subtypes) in diseased livers.

Some major references.

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Abbreviations.

HCA: hepatocellular adenoma; **H-HCA:** HNF1a inactivated HCA; **IHCA:** inflammatory HCA; **b-HCA:** b-catenin activated HCA; **b-IHCA:** b-catenin activated and IHCA; **UHCA:** unclassified HCA; **FNH**: focal nodular hyperplasia; **GSD**: Glycogen storage disease; **LFABP**: Liver fatty acid binding protein; **CRP:** C reactive protein; **GS:** glutamine synthetase; **ASS1**: Arginino succinate synthase 1; **HCC:** hepatocellular carcinoma; **vwd-HCC** : very well differentiated HCC; **OC**: oral contraceptives; **CEUS**: contrast enhanced ultrasound sonography; **NTL**: non tumoral liver

Figs. 1—5

Bordeaux HCA immuno-classification (218 surgical specimens)

Subtype	%	Diagnostic imaging	Main pathological features	IHC marker	Molecular biology
H-HCA	30	yes	steatosis/clear cells	**LFABP** # (lack)	biallelic inactivating mutation: *HNF1A* somatic: 90%; constitutional: 10%
IHCA	32	yes	sinusoidal dilatation, inflammation, thick arteries, pseudo-portal tracts	**CRP** #/SAA (overexpression)	IL6/JAK/STAT activation: mutations (80%): *IL6ST* (gp130) 65%, *FRK*, *STAT3*, *GNAS* or *JAK1*
b-HCA*	10 (6 ex3; 4 ex 7/8)	no	atypia (inconstant) many vessels no specific criteria	**GS**# (diffuse/strong if exon 3 *)	*CTNNB1* activating mutations/deletions: different levels of b-catenin pathway activation depending the mutation type: exon 3 or 7/8
b-IHCA*	14 (9 ex 3; 5 ex 7/8)	*associated criteria (imaging, pathology, IHC, molecular) of b-HCA and IHCA*			
ASS1+HCA° including shHCA°	10	no	bland pattern; various degree and stage of hemorrhage and vessels abnormalities	**ASS1**# •• (overexpression T/NT) all other specific HCA markers negative	*GLI1* activation (INHBE-GLI1 fusion) Sonic Hedgehog activation
UHCA▪	4	no	not specific	all negative or not diagnostic	no identified mutations

used in practice to routinely classify HCA *high risk of malignant transformation if exon 3 mutations (3-4%) ° high risk of symptomatic bleeding *except exon 3 S45 (« starry sky pattern); weak in exon 7/8; both often limited by a GS border, with diffuse CD34 in b-HCA, except at the border. **discovered by proteomics analysis
Risk factors: estrogens for all HCA subtypes, obesity for IHCA and ASS1+HCA, androgens and male sex for b-HCA and b-IHCA, liver vascular diseases for malignant transformation of all HCA subtypes ▪ include HCA with no specific marker and HCA that cannot be classified (hemorrhage, necrosis/no sufficient viable tissue)

Figure 1 Bordeaux hepatocellular adenomas (HCA) immuno-classification (a synthetic view of 218 surgical specimens).

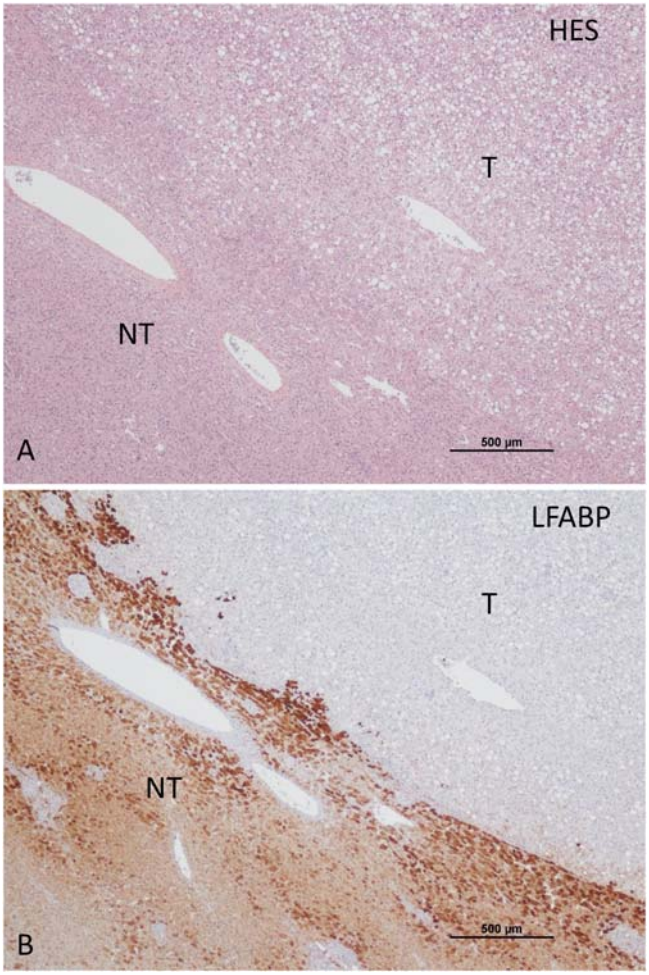

Figure 2 H-HCA — Benign hepatocellular tumor (T) with diffuse steatosis (A), lacking of LFABP in T contrasting with normal expression in non-tumoral (NT) liver (B).

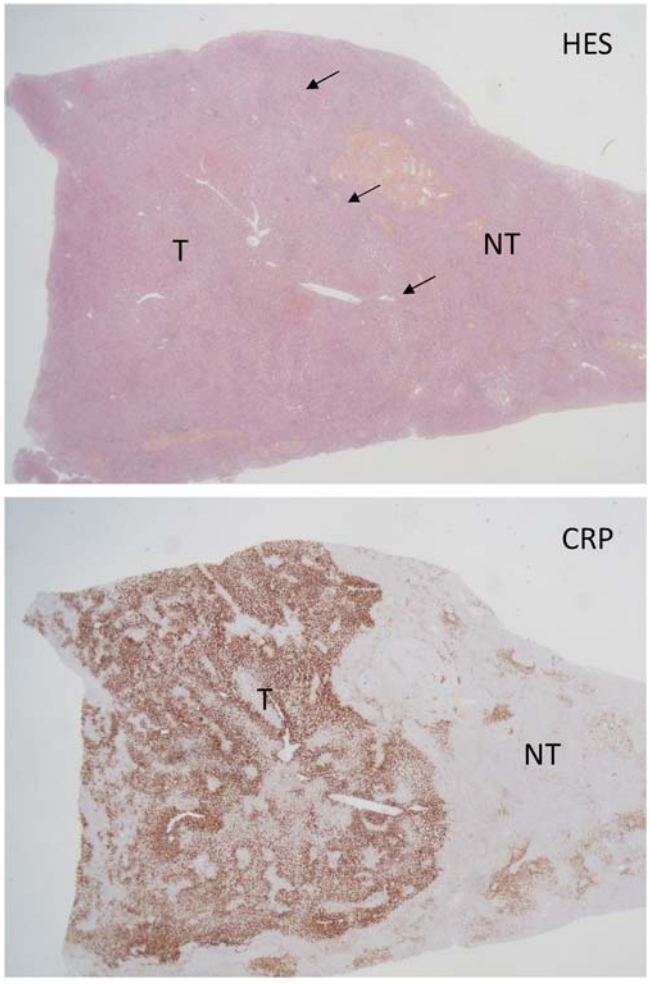

Figure 3 IHCA — Ill defined (arrows) benign hepatocellular tumor (T) without typical criteria on H&E (A), but highlighted by strong CRP overexpression with marked demarcation from NT (B).

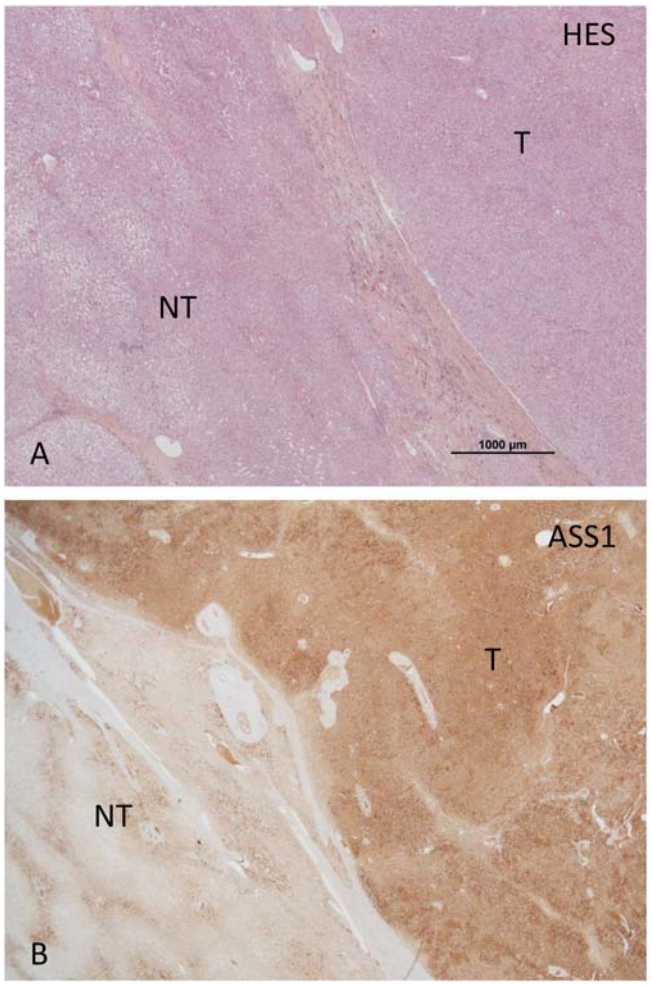

Figure 4 ASS1 + HCA — Benign hepatocellular tumor (T) with a bland aspect (A), overexpressing ASS1, in comparison with steatotic NT (B).

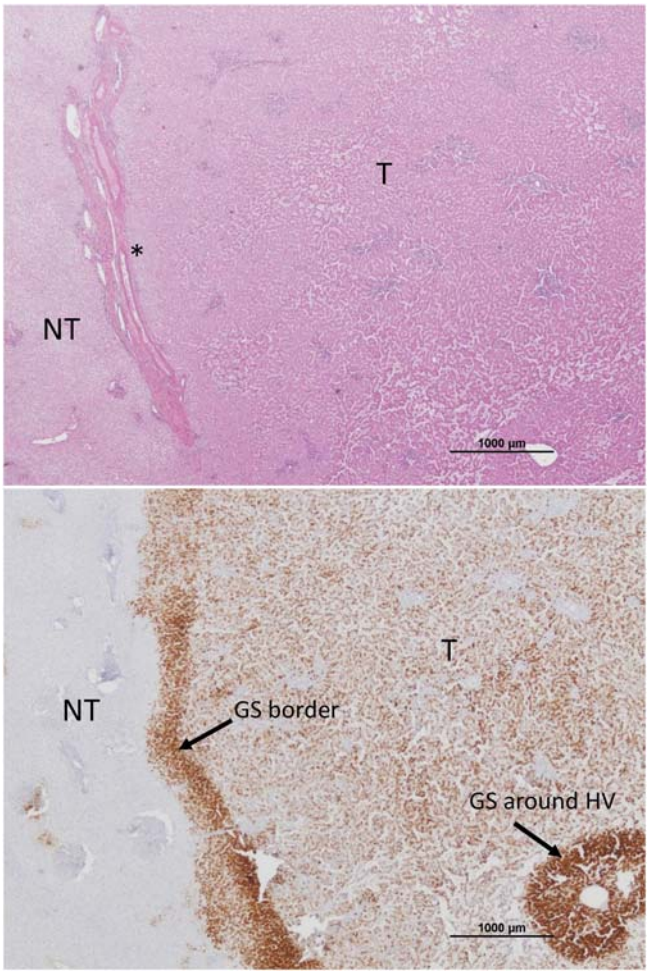

Figure 5 b-IHCA exon 3 S45 mutated — Benign hepatocellular tumor (T) with a thin border (asterisk) already visible on H&E (A), strongly expressing GS whereas GS in the T has a heterogeneous ''starry sky'' pattern (B). CRP is positive including the border (not shown).

Contribution

The idea was conceived by C. Balabaud and P. Bioulac-Sage.

The draft was written by P. Bioulac-Sage, C. Balabaud and C. Sempoux.

All authors contributed to the final version.

Disclosure of interest

The authors declare that they have no competing interest.