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Repeat surgery in HNF1alpha-inactivated adenomatosis

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List of abbreviations

Hepatocellular adenoma (HCA)

HNF1a-inactivated HCAs (H-HCA),

HNF1a-inactivated adenomatosis (H-adenomatosis)

Inflammatory HCAs (IHCA),

β -catenin activated HCA (b-HCA),

β -catenin activated and inflammatory HCAs (b-IHCA)

Conflict of interest: No

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CB, PBS design the study and wrote the paper

CL, JFB, LC, NF, followed the patients

BLB, MCSP, and PBS performed the immunohistochemistry

LP is in charge of the data base

CB and PBS reviewed the slides

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Abstract

Background & Aims. Stopping oral contraceptives following nodule detection usually prevents further hepatocellular growth (HCA); rare cases of growth have been reported after surgery.

The aim of the study was to review our resected HCA cases and their outcomes and more specifically, growth.

Methods. We retrieved all HCA cases that required a second intervention and HCA growth cases of none resected HCA after resection of one or several HCAs.

Results. Out of the 210 resected classified HCA cases, a second resection was performed in 5 cases, 4 of which were in women with HNF1 α -inactivated adenomatosis (H-adenomatosis) and had a favorable outcome. The fifth case was the occurrence of an inflammatory HCA, 3 years after resection of a previous one. Of the 65 resected HNF1 α -inactivated HCAs (H-HCAs), the nodules that remained continued to increase very slowly in 3 adenomatosis cases. After surgery, the liver became dysmorphic years later in one case, and the nodules grew but not significantly in another case. After the diagnosis of adenomatosis, progressive growth leads to surgery 12 years later in the last case.

Conclusion. These results confirm that, in rare H-adenomatosis, size of nodules may increase very slowly, probably in part through coalescence of micro H-HCAs and leading occasionally to a second resection.

Key words: Hepatocellular adenoma; HNF1alpha -inactivated hepatocellular adenoma; adenomatosis; liver surgery

Key points

- Stopping oral contraceptives following nodule detection usually prevents further hepatocellular adenoma (HCA) growth.
- Rare cases of HCA growth have been reported leading eventually to a second intervention
- Growth is only observed in rare HNF1 alpha-inactivated adenomatosis
- Size of nodules may increase, probably in part through coalescence of micro H-HCAs.
- A second intervention due to HCA expansion has to be evaluated; liver transplantation is still not an option.

Background

Hepatocellular adenoma (HCA) occurs mainly in women taking oral contraceptives (OC) ¹⁻⁶. Additional factors such as obesity also play a role⁷. Outside the context of emergency, classically, surgery is performed for HCA ≥ 5 cm to prevent hemorrhage and malignant transformation complications ¹⁻⁶; HCA growth is rarely observed after stopping OC ¹⁻⁶. However, there are some cases of re-intervention reported in the literature due to *de novo* growth². Unfortunately, there is no indication on the subtype of these growing HCAs that may require a second resection. In this work, our aim was to study and provide a better overview of the phenotype of growing HCA during follow-up leading, occasionally, to re-intervention.

Material and methods

Between January 1988 and September 2017, 218 patients had resection for one or several HCAs in our department. All HCAs were classified using the phenotype classification⁸⁻¹⁰. There were 65 HNF1alpha inactivated HCAs (H-HCA), 71 Inflammatory HCAs (IHCA), 23 β -catenin activated HCA (b-HCA), 30 β -catenin activated and inflammatory HCAs (b-IHCA), 21 HCAs overexpressing ASS1¹¹. One patient with an ASS1+HCA had also 2 IHCA and was counted in the 71 IHCA list. Finally, 8 patients had unclassifiable HCAs (UHCA) due to massive necrosis and/or hemorrhage.

In our database, we retrieved surgical cases with single nodule, multiple nodules and adenomatosis (10 or more nodules identified by imaging) as well as cases with recurrence of new nodules or growth during follow up occurring after or before resection.

We retrieved cases with growth leading to re-intervention in 5 out of the 8 cases (excluding cases with pre-established surgery in 2 steps and cases with growth depending on malignant transformation).

No strict guidelines concerning the definition of growth observed on MRI was applied in this retrospective study. The rhythm of follow-up is also related to multiple factors (table 1). This study was approved by the local committee of “ Direction de la recherche clinique et de l’innovation” Bordeaux University hospital, Bordeaux Liver Biobank BB-0033-00036.

Results

The total number of resected HCAs according to a specific phenotype, number of nodules before surgery and patients with nodules still present after surgery is presented in table 2. It is interesting to note that growth before or after surgery leading or not to re-intervention was essentially observed in the group of H-HCA (table 2) and specifically those with adenomatosis. In our series of 65 H-HCAs, 27 cases had developed a single nodule, 23 cases with multiple nodules, and 15 cases with adenomatosis. In 24 cases, nodules were left over after resection (11 cases of multiple H-HCA and 13 cases of H-adenomatosis; table 2). The size of the nodules remained stable or decreased in all H-HCA cases but :

(i) In 3 cases, we observed growth during follow-up but not leading to re-intervention (table 3). In case 166, the biggest nodule in segment I was 20 mm in 1998, growing slowly (28 mm in 2000, 35 mm in 2011); Tumorectomies (segments I, IV and VI) were performed 13 years later (2011) and shown H-HCA nodules measuring 35, 40 and 15 mm, respectively. In case 22, the nodule in segment I was 40 mm in 1994 and was 75 mm in 2008; the surgeon was reluctant to remove the nodule for technical reasons. MRI in 2016 showed that the liver was dysmorphic with many steatotic areas with an ill-defined confluent heterogeneous mass and nodules of different size (difficult to measure precisely). A liver biopsy was performed in this specific area. On H&E, the biopsy contained intermingled tumoral (partly steatotic) and non-tumoral tissue. No fibrosis was detected. Lack of LFABP confirmed the H-HCA subtype.

In case 122, small H-HCA left over after surgery grew over time but not significantly from 2008 to 2015.

(ii) In 4 H-HCA cases, growth lead to re-intervention; the clinical, radiological, surgical and pathological data of these cases are presented in table 4. All four patients had H-adenomatosis and without MODY3 or vascular disorders. The second resection was performed after 9 years in two cases, 11 and 23 years, in the other two cases. Interestingly, in one case (case 82), the first resection was a right hepatectomy for an enormous adenomatosis, sparing the left lobe (imaging). Nine years later, new nodules were discovered in the left lobe. On the second resected specimen, at least one nodule was at the margin of first resection.

Finally, in our database, we found only one case of re-intervention not linked to H-HCA phenotype (case 72; table 4). The first resection (right hepatectomy) was performed in 2000 in a 53-year-old woman for a 15 cm acute hemorrhagic tumor with non-specific pathological criteria; CRP was expressed in the tumoral and non-tumoral liver. In spite of the absence of inflammatory criteria on H&E the diagnosis of IHCA was raised with the detection of IL6ST mutation. During follow-up, another nodule was discovered which was 15 mm in 2001, 30 mm in 2003 leading to a segmentectomy. This nodule was a typical IHCA (H&E, C Reactive protein positivity by immunohistochemistry), also IL6ST mutated.

Discussion

There is poor information in the literature related to HCA growth. When HCAs are detected, women often stopped OCs following which the nodules growth stopped or their numbers decreased or disappeared⁴. This seems to be the case mainly in IHCAs¹². In the absence of regression, large nodules (>5 cm) are usually resected. Growth of unresected nodules < 5 cm after OC cessation is rare, and therefore not well documented except in case of malignant transformation, mainly in b-HCA¹³⁻¹⁷ or when HCA occurred in specific conditions such as

an underlying liver disease (NASH, vascular diseases, GSD, etc) ¹⁴. In men, HCAs are resected whatever their size and subtype.

In one of the largest series published², HCAs recurred or increased in size in 9 (8%) patients, aged 19 to 46 years. None of these 9 patients, with a follow-up period ranging from 15 to 134 months, experienced HCA complications. However, two underwent additional surgery for HCA enlargement >5 cm. On the other hand, regression and even disappearance of HCAs was observed in 4 (9%) out of the 45 patients with residual HCA after a follow-up period of 130 months (aged 37–59 years) ².

Our study showed that growth occurred, particularly in H-adenomatosis (corresponding to >10 nodules by imaging). We observed that true growth occurred in only 1 case (82, table 3). Surprisingly, the massive tumoral section was restricted to the right lobe of the liver¹⁹ and we noticed that the non-tumoral part, close to, contained multiple undetected micro H-HCAs. Unexpectedly, during follow-up, new nodules appeared in the remaining liver at the border of the resected liver. With time, those micro H-HCAs continued to grow albeit slowly (from undetected to a max of 35 mm in 9 years) (table 3 case 82) leading to a second intervention in another university hospital (Nice). The slow expansion/proliferation process is illustrated in the 7 H-adenomatosis cases reported in this series (tables 2 and 3)

Apart from true growth, it is important to outline that there is an additional possibility to explain the apparent growth. H-adenomatosis are composed of numerous nodules of different sizes and micro H-HCAs (in variable number), some in their immediate vicinity. Micro H-HCAs may coalesce with larger ones to form detectable nodules (by imaging)²⁰ and may lead, over time, to an apparent growth (Fig 1) ²¹⁻²². Coalescence could be due to arterial diversion more to the tumor than to the normal parenchyma in between two nodules. It is interesting to note that ultimately this arterial diversion may lead, as in case 22, to a dysmorphic liver.

Growth due to coalescence of nodules raises the difficult question of its significance in terms of complications and therapeutic strategy. When nodules are <5 cm there is no indication for surgery ⁴; nevertheless, re-intervention was performed in 2 cases (cases 82, 205; table 4). However, when nodules reach the 5-cm threshold, should they be resected? There are arguments to suggest that H-HCAs are less susceptible to bleeding than IHCAs ⁵⁻⁶, ASS1+ HCA ¹¹ or to malignant transformation compared to b-HCA, leading to the proposal that the 5-cm limit size could be overcome, especially in H-adenomatosis ¹² and in menopausal women. We propose that these patients should be carefully followed-up usually by ultrasound. If growth is very slow, patients should be reassured. In a review dealing with liver transplantation for liver adenomatosis, there were patients transplanted under the label “evolution”, meaning patients who had adenomatosis with progression in size or number of adenomas ²³. In our opinion, iterative resection could be a better alternative ²⁴. Only long-term follow-up of slow-growing H-adenomatosis will indicate if a “wait and see” attitude is reasonable. In addition to the risk of HCC transformation and bleeding, it is relevant to know the natural history of each HCA subtypes. We observed more and more H-HCAs in women far after menopause ²⁵.

Our series illustrates the rare observation of re-intervention due to the discovery of an IHCA few years after the resection of a previous HCA sharing the same mutation in a woman who has never taken oral contraceptives. In this case it is possible that the nodule that grew during follow-up was present but missed due to its small size. In any case this observation of IHCA is probably exceptional (age of the patient, no oral contraceptives, growth)

This study is retrospective with no protocol to measure exactly the size of the nodules, the limit of detection of nodules, the rhythm and modality of imaging, the decision to operate and re-operate, the criteria to decide when the patient does not need to be followed. Furthermore it does not take into account the radiological improvement in the detection of nodules. In spite

of that, this study shows clearly that H-adenomatosis is more prone than any other subtypes to growth leading occasionally to re-intervention. This is due to its specificity in terms of the high number of nodules, the weak impact of stopping oral contraceptives on nodule size regression, the possibility of nodules coalescence. Growth as well as the justification of re-intervention needs to be confirmed by others.

In conclusion, patients with H-adenomatosis should be carefully followed for a long time period due to the possibility of growth leading occasionally to re-intervention.

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Figure Legends

Fig 1.

This patient (case 53) has multiple H-HCA (adenomatosis). After a first resection in 2001, it shows two close H-HCAs on H&E (left) with a small subcapsular nodule (A) close to a large nodule (B). A second resection was performed in 2010. On this LFABP staining (right), showing lack of LFABP in HCA, several H-HCA nodules are close to each other giving the impression of a single large one.

NT non tumoral liver.

HCA guidelines in Bordeaux liver center

Discovery of a single or several HCA (< 5 cm) ¹

Follow up (MRI)

resection

Rule: No follow-up after a satisfactory control at 2 years. This rule has been applied recently (2016). An ultra sound is recommended at 5 and 10 years.
Exceptions - Underlying liver disease : GSD ; vascular disease etc - incomplete resection - HCA with malignant transformation. Follow-up like in HCC
micro HCA (surgical specimen): in nodules remained undetected after 2 controls

No resection ²

Follow –up depends on size (> or < 2 cm) evolution during time (growth, stability or decrease).

Discovery of multiple nodules/ adenomatosis ¹

resection ²

All large nodules (>5 cm) are candidates for resection.

Multiple nodules/adenomatosis left after resection ²

All cases are followed as long as HCA continue to grow . Follow-up is stopped when size decreases and become smaller than 1 cm. with a control years later (5) . When size remains stable they are followed but with longer time interval

¹ stop OC

² ; decision to operate or not (multidisciplinary liver team ; surgeon, radiologist, hepatologist, pathologist) depends on age, sex, size, location, etiology, mode of discovery, eventually subtypes (imaging, biopsy) .Major importance to know the subtype (immuno histochemistry)

08 10 2018

Table 2 - HCA with detectable nodules (imaging) still present in the liver after resection

Subtype	H-HCA	IHCA	b-IHCA	b-HCA	ASS1+ HCA
Number of patients	65	71	30	23	21**
Solitary Nodule	27	44	20	17	9
Multiple nodules (<10)	23	21	8	4	10
Pts with nodules left over after resection	11 (1*)	13 (1*)	6 (1*)	3	4 (2*)
follow up at 1 year	3	2	1	1	1
follow up at 2 years	4	5	2	0	1
follow up at 5 years	3	5	2	2	0
adenomatosis ≥ 10	15	6	2	2	2
Pts with nodules left over after resection	13 (3*)	6 (1*)	2	2	2
follow up at 1 year	2	2	0	1	1
follow up at 2 years	2	3	1	0	1
follow up at 5 years	6	0	1	1	0
re intervention	4	1	0	0	0
growth	3	0	0	0	0

*NA data for follow up ** one patient is in the IHCA list Pts: patient

Table3 - H-HCA adenomatosis growth during follow-up not leading to reintervention

Patient ID	Sex / year of birth/ age	OC Yes (years)/no	Date /age patient location,number n / size (mm)	Year surgery/ Age patient / type surgery	Resection location,number n /size (mm)	Theoretical number n left in the liver location	Years follow-up	Year surgery/age patient Surgery/number, location/ size (mm) of n
166*	F/1965	Yes (10)	1998/ 21 adenomatosis largest VII, VIII/ 26mm seg I/ 28 mm (2000)	No surgery			13	2011/46 LH + I /35 + tumorectomy IVB /40 ; VI /15
22	F/1967	Yes (10)	1994/ 27 adenomatosis 3 nodules IV/ 60; VII/80 seg I / 40	1994/ 27 / RH + IV	-IV /60 -VII/ 80 -V /3 little HCA Micro HCA	3 nodules/ 40 (seg I)	14	2008/ 41 seg I/75 (Increase in size started in 1997, stable since 2008) 2016 (MRI): dysmorphic liver with many small nodules.
122	F/1981	Yes (10)	2008/ 27 adenomatosis / LL /150	2008/ 27 / LL + V	LL/ 150 V/ 25 + micro HCA	multiple	7	2015/ 34 8 nodules / 20 VI/ 15 , 10

n nodule; RH right hepatectomy; LH left hepatectomy; LL left lobe; RHV right hepatic vein; LHV left hepatic vein

* 2009 endoscopic resection of a colon polyp. 2011 adenocarcinoma sigmoid : resection + chemotherapy.

Table 4 H-HCA adenomatosis growing leading to re-intervention

			Imaging prior surgery Number n and size (mm)	Surgery			Follow-up				
H-HCA											
Patient ID	Sex / year of birth	OC Yes (years)/ No	Date/age patient n: number / size mm	Year surgery/ age patient / type	n resection number/ location / size mm	Theoretical left n location/ size mm	Years follow-up	n: number/ location/ size Prior surgery	2 nd surgery Year/type	Removed n: number/ size mm	Other
50	F/1972	Yes (8)	2000/ 27 adenomatosis 6 n visible/ 35 + 1 FNH	2000/27 LH + I + tumorectomies	5 and several micro H-HCA seg I/ 60 (hem/necrosis) LH 40, 10 1 FNH	seg VIII / 28 VI FNH? HCA? 11mm	11	In between RHV and LHV/ 57	2011 tumorectomy	1 / 57 +micro H-HCA	RF 2002, Thyroid cancer 2012
53	F/1952	Yes (13)	2001/ 48/ adenomatosis VI / 60 Multiple lesions ≤ 30	2001/48 VI and IV	VI / 75 IV / 25 +micro H-HCA +micro n surface liver	many small different seg	9	5 n from 25 to 60	2010 seg III	1 / 60 + many micro H-HCA	
82	F/1978	No	2004 /26/ adenomatosis hepatomegaly, limited to the RL	2004/26 RH	the whole RL: tumoral intermingled with NTL calcifications. Resection R1	no tumor in the left liver	9	3 n 2 at the contact with resected RH	2013 IV / 35 nodule seg II	IV / 35 II / 7 + micro H-HCA NTL	
205	F/1971	No	1986/ 15 adenomatosis	1991/20 RH + resection LL	1/ 85 + 4 n (3 to 8)	many small	23	2008 IV /16, 10, 9 II /14, 6 2014 seg III (35 ; 25)	2014 / tumorectomies LL	37 38 (atypical) + micro H-HCA	

n nodule; RH right hepatectomy; LH left hepatectomy; LL left lobe; RHV right hepatic vein; LHV left hepatic vein; hem hemorrhage; RF radio frequency; NTL non tumoral liver