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ORIGINAL ARTICLE

Repeat surgery in HNF1alpha-inactivated adenomatosis



Charles Balabaud^{a,*}, Christophe Laurent^b, Nora Frulio^c,
Marie Christine Saint Paul^d, Brigitte Le Bail^{a,e},
Laurent Possenti^f, Jean Frédéric Blanc^{a,f}, Laurence Chiche^b,
Paulette Bioulac-Sage^a

^a Inserm, UMR1053 Bordeaux research in translational oncology, université de Bordeaux, Bariton, 33076 Bordeaux, France

^b Service de chirurgie digestive et endocrinienne, centre médico-chirurgical Magellan, Haut-Lévêque hospital, CHU de Bordeaux, 33604 Pessac, France

^c Department of radiology Magellan 2, Haut-Lévêque hospital, CHU de Bordeaux, 33604 Pessac, France

^d Pathology department, Pasteur Hospital, CHU de Nice, 06002 Nice, France

^e Pathology department, Pellegrin Hospital, CHU de Bordeaux, 33076 Bordeaux France

^f Department of hepato-gastroenterology and digestive oncology, Haut-Lévêque hospital, CHU de Bordeaux, 33604 Pessac, France

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KEYWORDS

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Summary

Background and 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 HNF1alpha-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-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.

* Corresponding author.

E-mail address: charles.balabaud@u-bordeaux.fr (C. Balabaud).

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.

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HCA	Hepatocellular adenoma
H-HCA	HNF1a-inactivated HCAs
H-adenomatosis	HNF1a-inactivated adenomatosis
IHCA	Inflammatory HCAs
b-HCA	β -catenin activated HCA
b-IHCA	β -catenin activated and inflammatory HCAs

Background

Hepatocellular adenoma (HCA) occurs mainly in women taking oral contraceptives (OC) [1–6]. Additional factors such as obesity also play a role [7]. Outside the context of emergency, classically, surgery is performed for HCA \geq 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 growth [2]. 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 classification [8–10]. 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 ASS1 [11]. 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

(Fig. 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 1. 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 1) 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 1). The size of the nodules remained stable or decreased in all H-HCA cases but 7:

- in 3 cases, we observed growth during follow-up but not leading to re-intervention (Table 2). 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;
- in 4 H-HCA cases, growth led to re-intervention; the clinical, radiological, surgical and pathological data of these cases are presented in Table 3. 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.

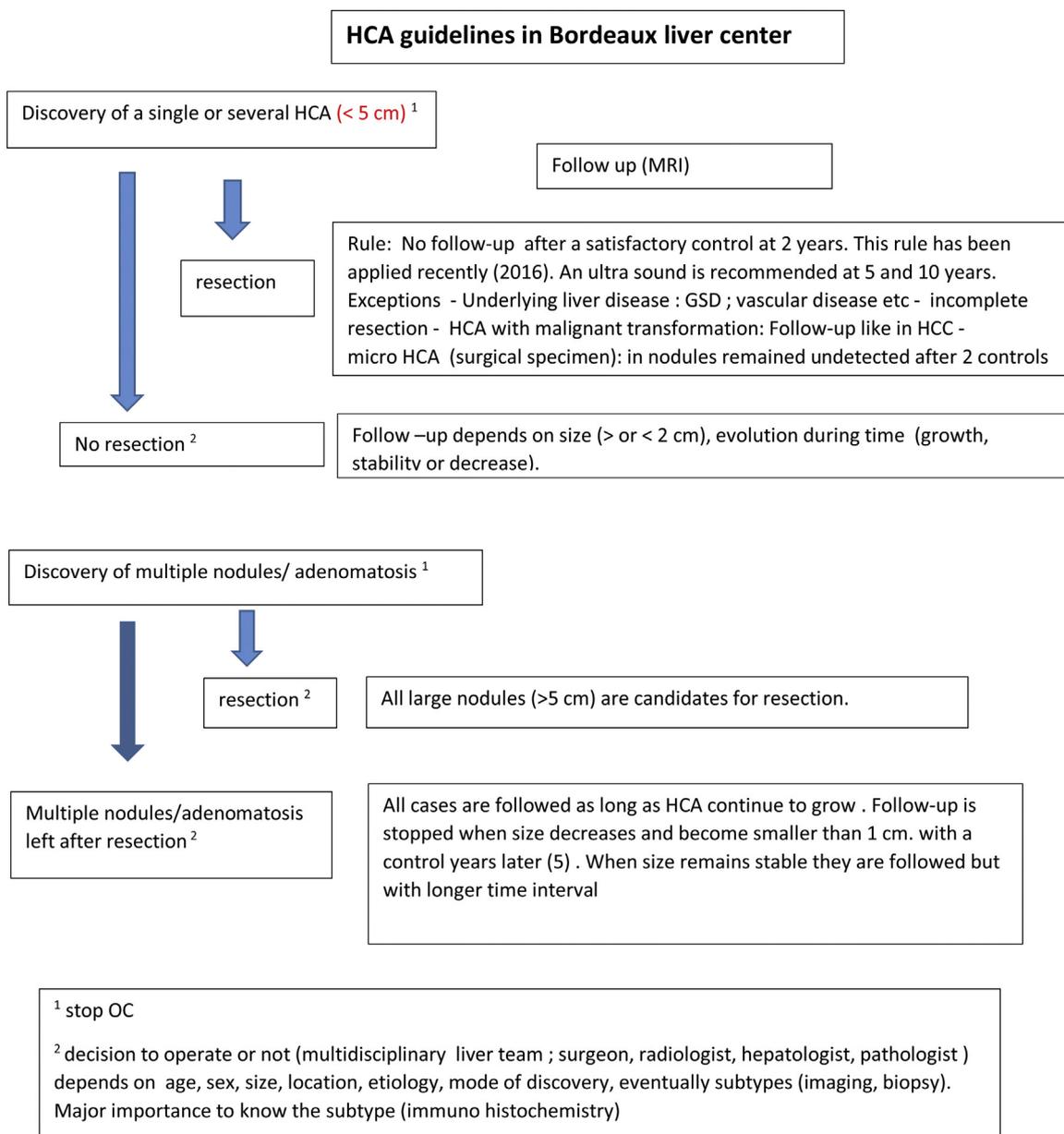


Figure 1 HCA guidelines in Bordeaux liver center.

Finally, in our database, we found only one case of re-intervention not linked to H-HCA phenotype (case 72; Table 3). 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 disappeared [4]. This seems to be the case mainly in IHCA [12]. 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-HCA [13–17] 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.

Table 1 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 ^b
Solitary nodule	27	44	20	17	9
Multiple nodules (< 10)	23	21	8	4	10
Pts with nodules left over after resection	11 (1 ^a)	13 (1 ^a)	6 (1 ^a)	3	4 (2 ^a)
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 ^a)	6 (1 ^a)	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

Pts: patient.
^a NA data for follow-up.
^b One patient is in the IHCA list.

In one of the largest series published [2], 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) [18]. We observed that true growth occurred in only 1 case (82, Table 2). Surprisingly, the massive tumoral section was restricted to the right lobe of the liver [19] 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 2, 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 1 and 2).

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. 2) [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 3). 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 IHCA [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

Table 2 H-HCA adenomatosis growth during follow-up not leading to re-intervention.

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 ^a	F/1965	Yes (10)	1998/21 Adenomatosis largest VII, VIII/26 mm 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.

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

Table 3 H-HCA adenomatosis growing leading to re-intervention.

Patient ID	Sex/year of birth	Imaging prior surgery Number n and size (mm)	Surgery	Follow-up							
				H-HCA							
		OC Yes (years)/no	Date/age patient n: number/size mm	Year surgery/ patient /type	age n resection number/ location/size mm	Theoretical left n location/size mm	Years follow-up	n: number/ location/ size Prior surgery	2nd 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 + 1 + tumorectomies	5 and several micro H-HCA seg I/ 60 (hem/necrosis) LH 40, 10 1 FNH	Seg VIII/28 VI FNH? HCA? 11 mm	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/ tumorec- tomies 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: radiofrequency; NTL: non-tumoral liver.

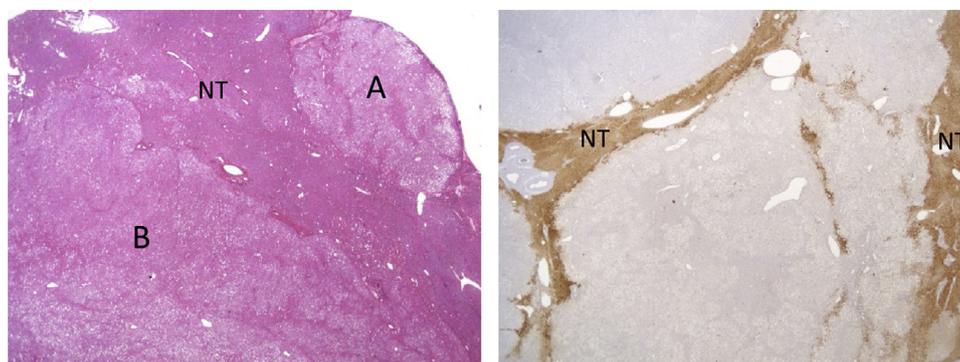


Figure 2 This patient (case 53) has multiple H-HCA (adenomatosis). After a first resection in 2001, it shows two close H-HCAs on H&E (left) with a small subcapsular nodule (A) close to a large nodule (B). A second resection was performed in 2010. On this LFBP staining (right), showing lack of LFBP in HCA, several H-HCA nodules are close to each other giving the impression of a single large one.

on nodule size regression, the possibility of nodules coalescence. Growth as well as the justification of re-intervention needs to be confirmed by others.

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.

Author's contributions

CB, PBS designed 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.

Funding statement

None.

Disclosure of interest

The authors declare that they have no competing interest.

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