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• *BRIEF REPORTS* •

Management of hepatocellular adenoma: Solitary-uncomplicated, multiple and ruptured tumors

Christian Toso, Pietro Majno, Axel Andres, Laura Rubbia-Brandt, Thierry Berney, Léo Buhler, Philippe Morel, Gilles Mentha

Christian Toso, Pietro Majno, Axel Andres, Thierry Berney, Léo Buhler, Philippe Morel, Gilles Mentha, Abdominal and Transplant Surgery, University Hospital, Geneva, Switzerland
Laura Rubbia-Brandt, Clinical Pathology, University Hospital, Geneva, Switzerland
Correspondence to: Christian Toso, Clinic of Digestive and Transplant Surgery, University Hospital, 24, rue Micheli-du-Crest, 1211 Geneva 14, Switzerland. christian.toso@hcuge.ch
Telephone: +41-22-3727702 Fax: +41-22-3727755
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AIM: While hepatocellular adenomas (HAs) have often been studied as a unique entity, we aimed to better define current management of the various forms of HAs.

METHODS: Twenty-five consecutive patients operated for solitary-uncomplicated (9), multiple (6), and ruptured (10) HAs were reviewed according to management strategies and outcomes.

RESULTS: All solitary-uncomplicated HAs (ranged 2.2-14 cm in size) were removed. Out of 25 HAs, 2 (8%) included foci of carcinoma. In the multiple HA group, previously undiagnosed tumors were identified during surgery in 5/6 cases. In three cases with multiple spread HA, several lesions had to be left unresected. They remained unmodified after 4-, 6-, and 6-year radiological follow-up. Patients with ruptured HA (ranged 1.7-10 cm in size) were initially managed with hemodynamic support and angiography, allowing the embolization of actively bleeding tumors in two patients. All ruptured tumors were subsequently removed 5.5 d (range 4-70 d) after admission.

CONCLUSION: Tumors suspected of HA, regardless of the size, should be resected, because of high chances of rupture causing bleeding, and/or containing malignant foci. Although it is desirable to remove all lesions of multiple HA, this may not be possible in some patients, for whom long-term radiological follow-up is advised. Ruptured HA can be managed by hemodynamic support and angiography, allowing scheduled surgery.

Key words: Liver; Adenoma; Management; Surgery

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Hepatocellular adenomas (HAs) are generally considered as a single clinical entity, because they share a common histological appearance. However, HA can present as single or multiple tumors to be investigated in an elective setting (usually after the discovery of a silent hepatic lesion), or acutely as ruptured tumors causing right upper quadrant pain and/or intra-abdominal bleeding. Although the characteristics of HA have been described by several studies, still some controversy remains on its management. The aim of the present study is to offer a practical approach to the treatment of HA based on the various presentation forms of the disease, i.e., solitary-uncomplicated, multiple, or ruptured tumors.

From February 1980 to March 2003, 667 adults over 16-year underwent liver resection at our institution. Among them, 25 patients (3.7%) with HA represented the study population. All patients with a liver tumor compatible with a HA were operated in our hospital. No extra patient was found in the records of pathology, hepatology, and radiology.

For the purpose of the study, the patients were classified as cases with solitary-uncomplicated, multiple, and ruptured HA on the basis of clinical presentations and radiological evidences. The solitary-uncomplicated and multiple HA groups included patients with HA, but without a clinical bleeding episode. Patients with ruptured HA had clinical evidence of bleeding.

Data related to clinical picture, radiology, surgery and pathology were collected and compared between each group. Follow-up was performed in the outpatient clinic.

Over a 23-year period, 25 patients with HA were identified and included in the study. All patients were operated upon for a total of 58 HAs. Nine patients had solitary-uncomplicated (36%), 6 multiple (24%) and 10 ruptured HAs (40%). There were 23 females and 2 males, with a median age of 38 years (range, 19-55 years).

Clinical presentation

Signs and symptoms are summarized in Table 1. In the

Table 1 Clinical presentation of different forms of HA

	Solitary-uncomplicated HA	Multiple HA	Ruptured HA	Total
Cases (*n*)	9	6	10	25
No. of HA[1]	9	>39[2]	10	>58
Symptoms (no. of cases)				
None	3	3	0	6
Pain	6	3	10	19
Nausea / vomiting	3	0	5	8
Diarrhea	0	0	2	2
Asthenia	1	1	0	2
Median duration of symptoms (wk)[3]	8 (1-24)	5 (2-16)	1 (0.5-2)	2
Signs (no. of cases)				
None	6	5	0	11
Tenderness	3	1	10	14
Fever	2	0	4	6
Hepatomegaly	0	1	0	1

[1]Hepatocellular adenoma; [2]two patients presented more than 10 HA (adenomatosis); [3]median duration of symptoms up to diagnosis, excluding asymptomatic patients (three solitary-uncomplicated and three multiple HA).

solitary-uncomplicated and multiple HA groups, six patients (3/9 and 3/6, respectively) had no symptoms. Tumors were discovered because of increased liver function tests (LFT) in two, hepatomegaly in one, during laparotomy in one or at ultrasonography done for other reasons in two patients.

Twenty-two of the twenty-five patients (88%) were or had been taking exogenous sex hormones for a median duration of 9.25 years (range, 3 mo-22 years). They were equally distributed between all groups.

Laboratory findings

Seventy-two percent (18/25) of the patients had at least one increased LFT. Anemia and increased transaminases were more often associated to ruptured HA, while increased alkaline phosphatase and γ-glutamyl transpeptidase to solitary-uncomplicated and multiple HA (Table 2). Prothrombin time, albumin, and bilirubin were normal in all patients. α-Fetoprotein was normal in all nine patients in whom this marker was tested, including the two cases of HA with foci of hepatocellular carcinoma.

Table 2 Results of laboratory tests

Laboratory test (range)	Solitary-uncomplicated HA (9 cases)	Multiple HA (6 cases)	Ruptured HA (10 cases)
Anemia (Hb<12 g / dL)	4	2	7
Bilirubin (>25 μmol / L)	0	0	1
ALP (>125 μmol / L)	4	4	1
AST (>42 U / L)	0	0	4
ALT (>42 U / L)	0	0	4
γ-GT (>35 U / L)	5	3	4

ALP: alkaline phosphatase; AST: aspartate aminotransferase; AST: alanine aminotransferase; γ-GT: γ-glutamyl transpeptidase.

Radiological investigations

Ultrasonography was performed in 23 cases. Abnormal findings (a focal lesion or a hematoma) were detected in all cases, but a diagnosis of HA could never be established by ultrasonography alone. Computer tomography (CT), angiography, and magnetic resonance imaging (MRI) demonstrated possible images of HA in 3/25, 2/18, and 3/9 patients, respectively. Needle biopsy gave the correct diagnosis in five of eight cases who underwent this procedure.

Among the 10 patients with ruptured HA, no clear tumor could be identified by preoperative imaging in 7 cases, and the diagnosis of HA remained presumptive until gross examination of the resection specimen.

In patients with solitary-uncomplicated or multiple tumors (i.e., excluding patients with ruptured tumors), a correct pre-operative diagnosis could be made with radiology or liver biopsy in 9/15 cases.

Clinical management

The indication for surgery was either the presence of a possibly malignant tumor, or the preoperative diagnosis of HA. Liver resections were performed according to the principles of segmental surgery, with Kellyclasy or the ultrasonic dissector[1]. Intra-operative ultrasound was routinely performed to clarify the anatomical relationship of the known lesions and to guide the resection when the tumor could not be identified with certainty on preoperative imaging.

Patients with solitary-uncomplicated HA All the nine patients with solitary-uncomplicated HA required less extensive resections as compared to the patients of other groups (Table 3). Two HA patients (6.4 and 11.2 cm in tumor size) with tumor appearing heterogeneous on gross inspection demonstrated foci of hepatocellular carcinoma on frozen sections. In one of these patients, a local excision was extended for right hepatectomy after the results of the frozen sections. Both results on frozen section were further confirmed on paraffin-embedded sections.

Patients with multiple adenomas In these six patients, no clear diagnosis could be made before surgery, and intra-operative ultrasonography and frozen sections were performed in order to resect the largest lesions or the one most likely to be malignant. In five cases, previously unidentified tumors were discovered during the operation. In these patients, resections were extensive, involving three segments or more in four cases. A vascular exclusion maneuver was required more often in multiple HA group compared to the other groups (four hepatic inflow occlusion and one total vascular exclusion). In three cases with multiple

Table 3 Surgical management of different forms of HA

	Solitary-uncomplicated HA	Multiple HA	Ruptured HA	Total
Types of operation				
Enucleation	3	2[1,2,3]		5
Segmental resection	1	1[2]	2	4
Left hemihepatectomy	1		3	4
Hemihepatectomy (R)	4	4	4	12
Extended hemihepatectomy (R)			1	1
Median tumor size (cm, range)	6 (2.2-14)	3.05 (1.1-4)	7 (1.7-10)	5.25
Vascular exclusion (number of cases)	3	5	1	8
Median per-operative transfusions (*n*, range)	0 (0-2)	0 (0-4)	3 (1.7-10)	1.5
Median time between admission and operation (*d*, range)	3	3	5.5 (4-70)	
Median duration of post-operative hospital stay (*d*, range)	8 (6-15)	13 (7-20)	9 (8-28)	9
Complications				
Pleural effusion / atelectasis / pneumonia	1	2		3
Biliary leak		1	1	2
Pulmonary embolism			1	1
Coma	1			1

[1]Seven enucleations performed in the same patient; [2]performed in the same patient; [3]performed in an elective setting.

HA, several lesions were left unresected, and they were subsequently followed-up by yearly CT or MRI.

Patients with ruptured HA None of the 10 patients with ruptured HA was in hypovolemic shock on admission. The early management included hemodynamic monitoring and in two cases, transfusion of packed RBCs (two units in each patient). An angiography was performed in all cases of ruptured HA and in two, a vessel bleeding actively within liver parenchyma was identified and embolized. In all cases of ruptured HA, resection was delayed for a median of 5.5 d (range, 4-70 d) after presentation. In all cases, a hematoma was present in the tumor (two cases), in the liver parenchyma (six cases) or intraperitoneally (two cases). The risk of rupture was not associated with the size of the HA, and the ruptured HA ranged between 1.7 and 10 cm in size. The mean number of packed RBCs required during the operation was higher in the ruptured HA group compared to the others (Table 3).

Follow-up

The length of hospital stay was similar in all groups. There was no peri-operative death. The overall peri-operative complications rate was 28% (7/25), including three lung infections, two bile leakage (one in multiple HA and one in ruptured HA), one pulmonary embolism and one transitory coma of unknown origin, possibly due to a gas embolism on withdrawal of a central line. Both patients with foci of hepatocellular carcinoma were followed-up with a yearly CT during first 2 years and every second year thereafter, and were found to be disease-free for 2 and 11 years after surgery and without adjuvant treatment. In the three patients with multiple HA left unresected, no growth of lesion or new tumor appeared after 4, 6, and 6 years of follow-up, respectively. All other patients did not demonstrate any tumor recurrence.

The present study describes the management of the three modes of presentations of HA, such as solitary-uncomplicated, multiple, and ruptured tumors, in a series of 25 consecutive patients operated for 58 HAs.

HAs are rare tumors, representing 3.7% of all liver resections performed during the same period in our center and 10-25% of all operated benign tumors in other studies[2-4]. The various forms of presentation are often studied together according to the common pathological appearance rather than as separated clinical entities with specific presentations and deserving specific management. In addition to the solitary-uncomplicated cases, 12-42% of HA present acutely as ruptured tumors[3-5] and 8-36% are multiple tumors often requiring complex surgical decisions and procedures[3,6-10].

Management of solitary-uncomplicated HA

We defined solitary-uncomplicated HA as single adenomas without clinical or pathological evidence of bleeding on gross examination of the cut surface. In this group, the clinical challenge is the appropriate management of a solitary liver nodule and its differential diagnosis with other tumors, such as hemangioma and focal nodular hyperplasia, which, in contrary to HA, do not require surgical removal. Symptoms are non-specific, including pain that is rarely acute[2,7,10-12]. In one-third of the cases, the tumor is silent and discovered incidentally[2,11]. While LFTs are increased in many patients in the present study, they are most often normal, and do not help to identify the tumor[2,7,12,13].

Radiological investigations play a key role in detection of HA. Due to the wider use of ultrasonography to investigate a variety of abdominal conditions from uncomplicated pregnancy to non-specific abdominal pain, an increasing number of focal liver tumors are discovered accidentally. Diagnosis of HA remains difficult, with accurate tumor characterization in only 50-70% for CT, angiography, and scintigraphy[4,13,14]. These results can be explained by the highly variable radiological behaviors of HA according to the presence of steatosis, necrosis, bleeding, or malignant transformation, as well as by the similarities to some cases of focal nodular hyperplasia and fibrolamellar hepatocarcinoma. MRI appears to be more effective, and identifies HA in 75% of cases[8,12,13,15]. In the present study, the low preoperative diagnostic accuracy is explained by the long study period and the use of radiological examinations with low accuracy

for the initial patients.

In our institution, all patients suspected of having HA were operated and the outcome of conservative management could not be assessed. This is an important issue, as some studies advise resection of HA only, when they are larger than 5 cm, because of the tendency of regression of smaller HA[4,10,16,17]. However, only half of these tumors were found to regress on long-term follow-up[4], and we believe, together with others, that adenomas should be removed with an open[2,7,18,19] or laparoscopic approach[20,21], regardless of size. HA generally occur in young patients without hepatocellular dysfunction, and a resection, even major, has a mortality rate lower than 1%[2,4,6,9]. On the contrary, after rupture, resection is more complex, transfusion requirements increase and overall mortality figures up to 10% have been quoted[22-24]. Furthermore, foci of hepatocellular carcinoma have been identified within HA of any size with a prevalence of 4-16% of the cases[3,10,18,25], probably a conservative estimate, as later stages of malignant transformation can no longer be recognized as originating from HA and are diagnosed as *de novo* carcinomas. The follow-up of HA is also difficult because malignant transformation can appear without increase in size, and the tumor marker α-fetoprotein has low sensitivity[4,10,12,18,25]. Finally, the occurrence of rupture is not related to the size of HA, and can happen, as shown in our series, in HA as small as 1.7 cm.

Management of multiple HA

Multiple HAs pose a diagnostic and therapeutic challenge. A malignant lesion is difficult to be ruled out, excluding the possibility of conservative management, and in some cases, the totality of the lesions cannot be removed. Two options remain open: liver transplantation or surgical exploration with resection of the largest lesion. Transplantation is required in some symptomatic patients[9], in cases of massive or multifocal lesions, especially with an underlying metabolic disease[2,5,6,26-28]. In the other cases, such as the patients of this study, surgical exploration should be preferred, because of its lower morbidity[5,6,27]. The direct examination of liver and intra-operative ultrasonography often discover new tumors (5/6 cases in this study)[2-12]. Frozen section should be performed because of its superiority over fine needle biopsies in diagnosing the type of tumor, and its high consistency, as seen in our study, with the paraffin-embedded histological results. After identification of all tumors, if removal of all lesions is not possible, we advise surgical resection of the largest and most heterogeneous ones, and yearly radiological follow-up of the remaining lesions. In this study, three patients with unresected lesions were symptom-free without increase in tumor size after a follow-up of 4, 6, and 6 years, respectively. In cases of symptomatic patients or of tumor relapse, a further resection or transplantation should be considered.

Management of ruptured HA

Patients with ruptured HA do not represent a diagnostic challenge, because the association of acute abdominal pain (all patients in this group), increased LFTs and radiological evidence of intrahepatic or intraperitoneal bleeding often point to the diagnosis of a ruptured hepatic tumor. The differential diagnosis between a bleeding HA and hepatocellular carcinoma remains difficult in some cases, but hepatocellular carcinoma is rare in young women without underlying liver disease. The early management of all spontaneous hemorrhages, regardless of tumor origin, is the same with hemodynamic monitoring and support. Most patients are stable on admission and require only intravenous fluids and occasionally blood transfusions[22,24,29]. Rarely, patients in shock may require emergency laparotomy[29]. Angiography should be performed as soon as possible: it allows the control of a possible actively bleeding vessel (two patients in our series), and a better identification of the lesion and its blood supply, which can be helpful to establish the surgical strategy. Resection can be postponed to later in the hospital stay, when the patient has fully recovered from the bleeding episode, to minimize the surgical morbidity and to allow the contralateral part of the liver to increase size, if embolization has been performed[22,24,29,30].

In summary, the present study describes the specific presentations and managements of the different types of HA. Tumors diagnosed as or suspected of being HA should be resected, regardless of their size. Multiple tumors should be explored surgically by performing intra-operative ultrasonography and frozen sections, which are mandatory to solve the differential diagnosis of hepatocellular carcinoma and other malignant tumors. Ruptured HA are managed primarily with hemodynamic support and angiography, followed by scheduled resection.

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