Focal nodular hyperplasia and hepatocellular adenomas: What is new in 2013?

Elisa Palladino, Daniele Sommacale, Renaud Siboni, Christine Hoeffel, Christian Lechner, Tullio Piardi, Reza Kianmanesh

ABSTRACT

Introduction: The history of benign liver cell tumors, namely, focal nodular hyperplasia (FNH), and hepatocellular adenoma (HCA), has recently progressed thanks to molecular biology and imaging studies that made it possible a new classification used in European, American and East countries. Case Report: A review was performed of the numerous published articles, with focus on the management and clinical outcome of benign liver cell tumors is an attempt to promote more standardized guidelines. Conclusion: The discovery of genetic drivers of HCA has refined our knowledge of the life history of HCA from risk factors of malignant transformation. The clinical management of FNH and HCA have changed in the recent years. This will have an impact on the management of these lesions including surveillance.

Keywords: Focal nodular hyperplasia, Benign liver cell tumors (BLCT), Liver lesions, Hepatocellular adenoma

INTRODUCTION

Benign liver cell tumors (BLCT) are common and their clinical management remains controversial. The differential diagnosis of liver tumors requires understanding of the clinical and imaging features of the liver lesions [1, 2]. A detailed history, physical examinations, hepatic tests and imaging studies are necessary for diagnosis. The use of liver biopsy, therapeutic options and follow-up are decided by the presentation of the lesion and associated patient characteristics. We present this review of literature with emphasis on the management of benign liver cell tumor with a multidisciplinary approach.

FOCAL NODULAR HYPERPLASIA

This is the second most prevalent benign liver lesion (after hemangiomata), with a woman preponderance, in 80–90% of the cases, in third or fourth decade and a global incidence of about 0.6–3% of the general population. It is no identifiable etiologic factor. It is, however, associated with a conditions having local or systemic vascular anomalies.
Focal nodular hyperplasia (FNH) has a demographic variation with a male and children of either gender preponderance in countries where oral contraceptives use has been less prevalent (i.e., China). There is not the impact on size variation from oral contraceptives use and from pregnancy and is not indispensable, though recommended, to stop oral contraceptive use [3].

Most of the patients are not symptomatic and the diagnosis is made incidentally during surgery, autopsy or imaging procedures for others symptoms. The liver function tests is normal complications, as the rupture, bleeding or malignant transformation, although rare, are described in literature [4].

The diagnosis of FNH can be made using imaging techniques in 90% of cases in experienced centers [5, 6]. Today, surgery and biopsy are performed in some academic centers in Europe and United States for diagnosis of FNH.

Contrast-enhanced ultrasonography (CEUS) is the first modality of choice for FNH:FNH typically shows arterial increased enhancement, very marked in the first few seconds. Centrifugal (70%) or eccentric (30%) enhancement through one afferent correspondingly situated arteries is a diagnostic pointer.

In the portal venous phase FNH shows at least low-grade increased enhancement in about 95% of cases. The centrifugal filling sign is very useful for diagnosis of FNH [7, 8].

Recently in 2013, Wang et al. from the University of Guangzhou (Republic of China) published their experience with CEUS in 85 patients with 85 histological proven FNH. Enhancement, centrifugal filling, spoke-wheel arteries were reviewed and correlated with the size. Forty-seven other focal liver lesions with contrast-enhanced computed tomography (CECT) were randomly selected for comparison of diagnostic with CEUS.

The results confirm that the CECT have similar diagnostic performance for FNH (Figure 1A) and CEUS should be the first imaging technique for the diagnosis of FNH [9].

The magnetic resonance imaging (MRI) scan has the advantage of being a non-radiating technique and has the excellent contrast resolution. In MRI, a typical FNH is hyperintense in the arterial phase and isointense before and in the portal venous phase (Figure 1B–C). In 89% cases, before contrast FNH is hyperintense to isointense on T2 and isointense to hypointense on T1 [10, 11, 12].

Half of FNH has a central scar, slightly hyperintense on T2 and isointense to hypointense on T1 [10, 11, 12].

HEPATOCELLULAR ADENOMA

This is an uncommon benign liver lesion arising from monoclonal proliferation of hepatocytes with a female preponderance before menopause and after a long-term use of oral contraception. It is associated with the duration and type of oral contraceptives usage. Other risk

appearing hepatocytes and must be supplied by altered portal tracts. The risk of complications as hemorrhage and malignant transformation is absent and surgery is not indicated. However, it is still performed for organ compression, compression of liver vessels and biliary tract, pain and especially if doubt about the nature of the tumor in the absence of histological diagnosis. To date, the unavailability of guidelines hampers the follow-up of these lesions. Regarding the management and treatment of FNH, we can summarized as follow:

If the patient is female with typical FNH on imaging, normal liver tests and no medical history of cancer, the diagnosis of FNH is considered and the biopsy is not necessary.

If the patient is a male, biopsy is proposed. In the case of atypical FNH on imaging biopsy is necessary [15]. FNH is often asymptomatic and the surgery is not indicated even if the large lesion. However, the patients with a large lesions can to develop abdominal pain or compression of adjacent structures and liver resection may be indicated. Laparoscopic enucleation without coverage of the resection margins is a contemporary approach. Relating to surveillance Cherqui D [16] published a short report on clinical management of benign liver cell tumors and it is proposed for FNH monitoring by a MRI to six and twelve months, then MRI or CEUS each year for three years; after to stop monitoring [16].
It is very important that HCA with activating mutation of β-catenin have a high risk of malignant transformation in HCC compared to other subtypes [28]. It should know that distinguishing HCA from well-differentiated HCC developed on normal liver could be challenging to diagnosis. Consequently, all patients identified with a mutation of β-catenin should be considered for liver resection to avoid the risk of malignant transformation.

- The third subgroup: Hepatocellular adenomas with inflammatory features (IHCA).

Inflammatory HCA presented a cytoplasmic over-expression of SAA and CRP, two proteins of the acute phase of inflammation, in the tumor hepatocytes (Table 1) [29].

IHCA is associated frequently with high alcohol consumption and obesity, two conditions associated with chronic cytokine production and it occurs often in woman [30].

- The fourth subgroup: Ten percent of HCA no identifiable etiologic factor (Table 2).

Pratical guidelines for the diagnosis of HCA subtypes are summarized in Figure 2.

| Table 1: Diagnosis of FNH performed in different academic centers |
|---------------------------------------------------------------|
| Ville | FNH | No Final Diagnosis |
|-------|-----|-------------------|
|       | Surgery | Biopsy | Surgery | Biopsy |
| French |
| Besancon | 13 | 3 | 0 | 0 |
| Bordeaux | 27 | 29 | 0 | 2 |
| Caen | 19 | 6 | 0 | 0 |
| Créteil | 19 | 13 | 0 | 0 |
| Grenoble | 3 | 12 | 0 | 1 |
| Lille | 25 | 39 | 2 | 6 |
| Lyon (1) | 17 | 16 | 4 | 7 (1 with HCC) |
| Lyon (2) | 14 | 22 | 0 | 4 |
| Montpellier | 15 | 25 | 3 | 1 |
| Nice | 3 | 25 | 3 | 1 |
| Paris (St.Antoine) | 20 | 14 | 0 | 2 (1 with HCC) |
| Villejuif (G.Roussy) | 5 | 6 | 0 | 4 |
| International |
| Baltimore (1984-2012) | 79 | 54 | 4 | 8 |
| Brussels Clinique Universitarie Saint Luc (1992-2012) | 22 | 14 | | |
Table 1: (Continued)

| Location               | FNH | No Final Diagnosis |
|------------------------|-----|--------------------|
| Heidelberg             | 34  |                    |
| (2007-2011)            |     |                    |
| London Kings           | 15  |                    |
| (1998-2011)            |     |                    |
| NY                     | 1   |                    |
| Mt Sinai               |     |                    |
| (2007-2011)            | 1    | 1                  |
| San Francisco          | 4   |                    |
| Seattle                |     |                    |
| Seoul                  | 15  | 17                 |
| Singapore              | 278 | 17                 |
| Taiwan                 | 45.4%| 32%               |
| Total nb %             | 335 | 278                |
|                        | 54.6%| 45.4%             |
|                        | 17   | 36                 |
|                        | 32%  | 68%               |

Figure 2: Criteria used for the identification of HCA subtypes (outside the emergency context)

**FNH**: Focal nodular hyperplasia. **HCA**: Hepatocellular adenoma. **IHCA**: Inflammatory Hepatocellular Adenoma. **H-HCA**: Adenomas inactivated for HNF1A. **B-HCA**: B-Catenin activated adenomas.
Table 2: Genotype/phenotype classification of hepatocellular adenomas

| Group                      | %     | Genetic        | Alteration                               | Pathway dysregulated                      | mRNA makers | Proteinmakers | Clinical Association                          | Histological phenotype          |
|----------------------------|-------|----------------|------------------------------------------|-------------------------------------------|-------------|--------------|-----------------------------------------------|----------------------------------|
| HNF1A-mutated HCA          | 30-40 | HNF1A          | Tumor suppressor gene                    | Activation of glycolysis, fatty acid synthesis and mTor pathway | Decrease LFABP1 | Lack of LFABP1 expression | Adenomatosis and association with MODY 3 diabetes (HNF1A germline mutation) | Diffuse steatosis                |
| CTNNB1-mutated HCA*        | 10-15 | CTNNB1         | Oncogene                                 | Activation of Wnt/catenin pathway         | Increase GLUL LGR5 | Overexpression of glutamine synthase and nuclear B-catenin | Risk of maligna transformation Male | Cell atypia and cholestasis       |
| Inflammatory HCA*          | 40-55 | IL6ST (65%) STAT3 (6%) GNAS (5%) Unknown (24%) | Oncogene                                 | Activation of JAK/STAT Pathway (oncogene-induced inflammation) | Increase SAA CRP | CRP Over expression | Obesity and high alcohol intake inflammatory syndrome | Inflammatory infiltrate Sinusoidal dilatation Dystrophic arteries |
| Unclassified               | 10    |                |                                          |                                           |              |              |                                               |                                  |

*50% of CTNNB1-mutated adenomas are also inflammatory*
Once the diagnosis of liver tumor is made, the patient is often referred to a surgeon (Figures 3 and 4). The identification of subtypes is one of the key factors among others that need to be collected.

There are neither specific guidelines nor a standardized therapeutic approach available to date to its management [31–33].

However, there is a consensus according to the HCA >5 cm should be resected if they have not regressed after stopping oral contraceptives, particularly those at a high risk of malignant transformation (β-HCA and β-IHCA) (Figure 4).

Some surgeons prefer that all HCA should be removed particularly, if they are easily accessible laparoscopically [34–36].

Balabaud C et al. from the University of Bordeaux, reviewed their experience and suggested the management of HCA subtypes <5 cm as it is summarized in Table 3 (Figure 5) [31].

They proposed in female patients, if size increases after follow-up and to stop oral contraceptive, resection if the size of lesion is >5 cm, though the resection should be considered for nodules <5 cm (in the 3–4 cm range) and resection independently of the size in the male. A biopsy is very performed in patients at risk of malignant transformation such as young woman/metabolic or vascular disorders. In presence of patients with H-HCA associated to abnormal genetic counseling resection should be considered independently of the size.

Future development will be based on imaging techniques, molecular data including chromosomal abnormalities, in the hope of being able to combine molecular, radiological and clinical data.

Table 3: Clinical and pathological information useful to manage the patient (Balabaud et al. 2013)

| Age, sex | Mode of discovery: emergency, pain, behavior after stopping (or not) Oral contraceptives |
|---------|------------------------------------------------------------------------------------------------------------------|
|         | Number of nodules, max size, location                                                                               |
|         | Radiological diagnosis: FNH, HCA, HCC, MRN, cannot differentiate                                                    |
| Woman:  | Oral contraception (age beginning, stop), duration, type, number of children (age)                                 |
| Drugs   | including all types of hormones particularly male, antiepileptic                                                 |
| Habit:  | alcohol, tobacco                                                                                                   |
| Vascular | diseases:                                                                                                          |
| Congenital malformations, BCS, HPSFam |                                                                                                                      |
| Biliary diseases: CHF, polycystic kidney diseases                                                                 |
| POCS    | Brain tumor                                                                                                        |
| Family history of liver tumors |                                                                                                                      |
| Pathological diagnosis: |                                                                                                                     |
| Biopsy, surgical specimen (safety margin) |                                                                                                                     |
| Biopsy: quality |                                                                                                                     |
| HCA: H-HCA, IHCA, B-HCA, B-IHCA, UHCA |                                                                                                                     |
| HCC     |                                                                                                                     |
| HCA borderline lesion; HCA with dysplasia, HCC foci |                                                                                                                     |
| FNH     |                                                                                                                     |
| FNH/UHCA |                                                                                                                     |
| FNH     |                                                                                                                     |
| MRN/FNH-like |                                                                                                                     |
| Association of different types of nodules |                                                                                                                     |
| Normal: steatosis, NASH, glycogenosis, vascular liver diseases, biliary disease and so forth |
Figure 5: Management of HCA subtypes < 5 cm

Pa - Patients overweight/obese/with metabolic syndrome (the majority with IHCA) should be followed

In presence of multiple HCA nodules: generally all nodules are of the same subtype (i.e., H-HCA, IHCA). Among IHCA some may be B-catenin mutated, others not. Association of H-HCA and IHCA has been rarely observed in a same liver. In glycogenosis, different types of nodules may exist (B-HCA, IHCA, B-IHCA and UHCA). The destruction (resection, radio frequency) of nodules depends on the size, on the presence of B-catenin mutation and on the disease background. OLT is exceptional and should not be considered just on the number criteria.

MODY 3: maturity onset diabetes of the young type 3, GS: glutamine synthetase
CONCLUSION

In future, we will be able to propose a specific guideline which can be a multidisciplinary approach (hepatologist, surgeon, radiologist and pathologist) towards the overall management of these diseases and is key factor for a good outcome.

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Author Contributions
Elisa Palladino – Substantial contributions to conception and designs, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
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Renaud Siboni – Substantial contributions to conception and designs, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Christine Hoeffel – Substantial contributions to conception and designs, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Christian Lechner – Substantial contributions to conception and designs, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Tullio Piardi – Substantial contributions to conception and designs, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Reza Kianmanesh – Substantial contributions to conception and designs, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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ABBREVIATIONS:

US: Ultrasound
MRI: Magnetic resonance imaging
CEUS: Contrast-enhanced ultrasound
NFH: Nodular focal hyperplasia
HCA: Hepatocellular adenoma
NRH: Nodular regenerative hyperplasia
BLT: Benign liver tumour
HCC: Hepatocellular Carcinoma
CT: Computed Tomography
OC: Oral contraceptives
GS: Glutamine synthetase
CRP: C-reactive –protein
IHCA: Inflammatory adenomas

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ABOUT THE AUTHORS

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**Elisa Palladino** is Resident at Department of General and Digestive Surgery of Chalons-en-Champagne Hospital, France. Her area of interest include liver surgery, gastrointestinal surgery, minimally invasive abdominal surgery. She has published research papers in national and international academic journals.

**Daniele Sommacale** is Professor at Department of General and Digestive Surgery, University of Reims, School of Medecine, France. His area of interest include hepatobiliary surgery and liver transplantation. He has published research papers in national and international academic journals and authored books.

**Renaud Siboni** is Resident at Department of Surgery, University of Reims, France. His area of interest include general surgery.

**Christine Hoeffel (MD, PhD)**, She is Professor of Radiology at the University hospital of Reims, France. She has published or co-published over 100 papers, mainly focused on abdominal imaging and magnetic resonance imaging.

**Christian Lechner** is Chief Resident at Department of General and Digestive Surgery of Chalons-en-Champagne Hospital, France. His area of interest include gastrointestinal surgery, minimally invasive abdominal surgery.

**Tullio Piardi** is Resident at Department of General and Digestive Surgery, University of Reims, School of Medecine, France. His area of interest include liver and pancreatic surgery, gastrointestinal surgery. He has published research papers in national and international academic journals.

**Reza Kianmanesh** is a Professor at Department of General and Digestive Surgery, University of Reims, School of Medecine, France. His area of interest include hepatobiliary and pancreatic surgery, liver transplantation, gastrointestinal surgery. He has published research papers in national and international academic journals and authored books.
