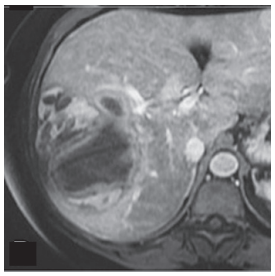

HEPATOCELLULAR ADENOMAS: CURRENT FINDINGS IN IMAGES WHICH ALLOW THEIR CHARACTERIZATION AND MANAGEMENT

ADENOMAS HEPATOCELULARES: HALLAZGOS ACTUALES EN IMÁGENES QUE PERMITEN SU CARACTERIZACIÓN Y MANEJO

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SUMMARY

Objective: The therapeutic approach of adenomas has changed in recent years, especially because of the possibilities for characterization by means of diagnostic imaging methods, mainly magnetic resonance imaging, which allowed us, in most cases, to approach the type of adenoma. ***Methods***: A review of the recent literature was conducted in order to describe the characteristic imaging features of the types of adenomas in the different imaging techniques, with an emphasis on MRI, which allows differentiation between histologic subtypes of adenomas. In addition, it also helps guide medical or surgical management. ***Results:*** In the literature, we described hepatic adenomatosis as an entity which is frequently found in women, with atypical imaging features. In addition, we mentioned the characteristics of MRI findings and their correlation with the types of adenomas, inflammatory, steatosic, β-catenin mutated and mixed. ***Conclusion:*** According to the classification based on genetic, histopathological and imaging features of the different subtypes of AHC, we could determine the natural history, define prognosis and the therapeutic options or imaging follow-up.

RESUMEN

Objetivos: El enfoque terapéutico de los adenomas ha cambiado en los últimos años, en especial por las posibilidades de caracterización por medio de las imágenes diagnósticas, principalmente la resonancia magnética (RM), que en la mayoría de los casos ha permitido una aproximación al tipo de adenoma. ***Métodos:*** Se realizó una revisión de la literatura reciente con el fin de describir las características imagenológicas de los tipos de adenomas, en las diferentes técnicas de imágenes, con principal énfasis en los hallazgos imagenológicos en resonancia magnética, lo cual permite diferenciar entre los subtipos histológicos de adenomas y ayuda a orientar el manejo médico o quirúrgico. ***Resultados:*** En la literatura se describe la adenomatosis hepática como una entidad frecuente en mujeres, de características imagenológicas atípicas. Además, se mencionan las características de los hallazgos por RM y su correlación con los tipos de adenomas, variedad esteatósica, peliótica y mixta. ***Conclusión:*** De acuerdo con la clasificación basada en las características genéticas, histopatológicas e imagenológicas de los diferentes subtipos de AHC y según la sintomatología, se podría determinar la historia natural y definir el pronóstico y las opciones terapéuticas o de seguimiento imagenológico.

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Introduction

Hepatocellular adenomas (AHC) are infrequent monoclonal hepatic benign neoplasia, made up of cells which simulate normal hepatocytes. They are mainly present in women who use oral contraceptives (ACO) for over two years (1,2).

From a genetic and pathological point of view, they are classified into three categories: inflammatory hepatocellular adenoma, associated with the mutation of the hepatocytic nuclear factor (FNH)- 1α and the adenoma associated with the mutation of the gene which codifies for β-catenin (table 1) (2).

Table 1. Classification and clinical characteristics, pathological and imaging of the different subtypes of hepatocellular adenomas

Molecular classification	Clinical characteristics	Histopathology	Characteristic by imaging
FNH-1 α mutation	Women, use of ACO, familiar hepatic adenomatosis, MODY 3.	Diffuse intra-tumor steatosis, L-FABP neg (protein which joins the fatty acids).	Loss of signal in out of phase signals.
Inflammatory	Young women, use of ACO, obesity, anemia, fever, increase in RFA. Presents a greater risk of bleeding.	PMN infiltrates, sinusoidal dilation.	High intensity with T2 information.
Mutation β-catenin	Men, use of hormones, glycogen deposit disease, familiar adenomatous polyposis. It presents a greater risk of CHC.	Sustained activation of β-catenin, which leads to cellular proliferation. Cytological anomalies, cellular atypia.	Without specific characteristics, it can simulate CHC. A central scar has been described.

Bioulac-Sage et al. (3) evaluated 128 adenomas, both genotypic and phenotypic, as well as the surgical point of view, which required the knowledge of the phenotypic classification of the lesion in order to define its management. This classification is important in order to achieve the complete characterization of these adenomas. The role of imaging evaluation has also proved to be useful for the characterization and detection of complications when using ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI); MRI is the most common and useful method.

Lewin et al. (4) evaluated patients with hepatic adenomatosis and concluded that there is a correlation between the MRI patterns and the three histopathological subtypes (steatosic, peliotic and mixed). These findings are related to the Bioulac-Sage et al. findings (3) and Laumonier et al. (5). Even though histopathological confirmation is necessary in order to determine the type of AHC, certain imaging findings also help characterize it.

They are usually solitary lesions, even though patients with two or more adenomas have been informed in literature. Described conditions such as hepatic adenomatosis are associated with more than 10 AHC (6-9).

Technical considerations

A multi-stage study is recommended for tomographic evaluation. This study must include a simple phase, where hepatic steatosis and hemorrhage are evaluated. It is administered through intravenous contrast medium, at a velocity of 3 ml/s, with acquisition in the arterial (25 s), portal (60 s) and tardy (>120 s) phase.

MRI studies for hepatic evaluation may be performed with 1.5 or 3 T systems. The protocol for the evaluation of focal injuries includes: a. Sequences with T2 information turbo spin echo axial and coronal. b. T2 axial information with turbo spin echo fat suppression. c. Sequences with echo gradient T1 information, phased and out of phase, which enable us to evaluate intercellular fat, which is essential for the classification of hepatic adenomas. d. Sequences with axial T1 information with echo gradient fat suppression (GRE), with sustained breathing, intravenous pre and post-contrast, with dynamic evaluation in the arterial, portal and equilibrium phase. In patients who have difficulty holding their breath, respiratory triggering techniques are used. e. Diffusion sequences with ADC, which is important for the evaluation of the entire hepatic focal lesion (10, 11).

Hepatocellular adenoma associated with mutation FNH -1α

It is the second most common subtype; it represents 30-35% of cases. It is associated with the familiar hepatic adenomatosis and MODY type-3 diabetes (maturity onset diabetes of the young). It is exclusively developed in women; in over 90% of cases, it is associated with the use of ACO. In 50% of cases, they are multiple lesions. Most of them are asymptomatic lesions, discovered as incidental findings (3,14).

A lesion with diffuse intra-tumor steatosis is found in the histopathological study (14). The CAT scan can show macroscopic fat content in only 7% of cases (15,16). In the MRI, they are high-intermediate signal lesions in sequences with T1 information, with a fall in the intensity of the signal in out-of-phase sequences due to the presence of intracellular steatosis (figure 3). Usually, it is associated with diffuse hepatic steatosis. Sequences with T2 information have an intermediate-high signal. The sensitivity and specificity of the content of intracellular lipids in AHC associated with FNH-1α mutation are 86 and 100%, respectively (2,5).

After the administration of extra-cellular contrast (gadolinium and iodine), these lesions show a moderate enhancement in the arterial phase, without a persistent enhancement in subsequent phases (table 2). This subtype of adenomas is the least aggressive, with a minimal risk of bleeding, rupture, and a minimum or no risk of developing malignancy (2).

Table 2. MRI characteristics of the different subtypes of hepatocellular adenomas

Subtype	T1 GE	T2	Contrasted T1
Mutation FNH-1 α	Isointense-high intensity. Loss of signal of an out of phase sequence.	Isointense-slightly hypertense.	Slight enhancement in the arterial phase. Without persistence in enhancement in the portal and tardy phase.
Inflammatory	Isotense-slightly high intensity. Without a loss in out of phase signal.	High intensity. Greater intensity in the periphery (atoll sign).	Intense arterial enhancement. Persists in the portal and tardy phase.
Mutation B-catenin	Without out-of-phase loss.	Without atypical characteristics.	Without a typical pattern. It may simulate CHC.

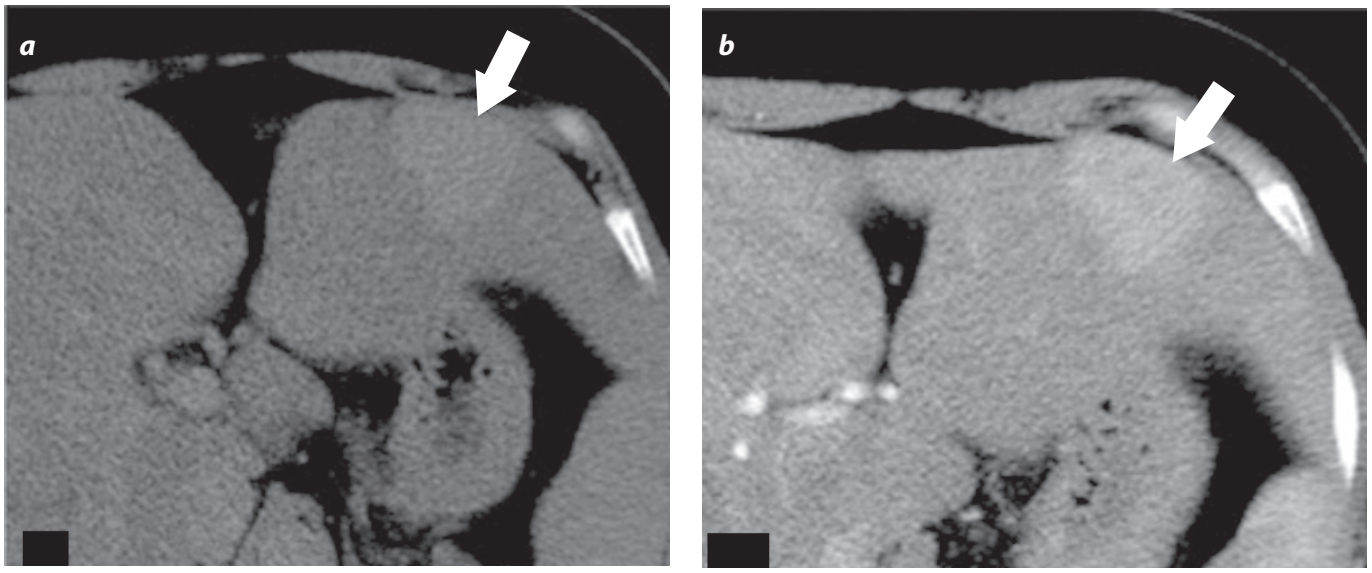

Figure 1. a) Computerized axial tomography in a simple phase; a reduction of hepatic attenuation by steatosis and a focal lesion in segment II can be seen, with high attenuation. b) Computerized tomography in the arterial phase; an intense enhancement of the lesion can be seen. The follow-up of the lesion showed its disappearance after the suspension of oral anovulatories.

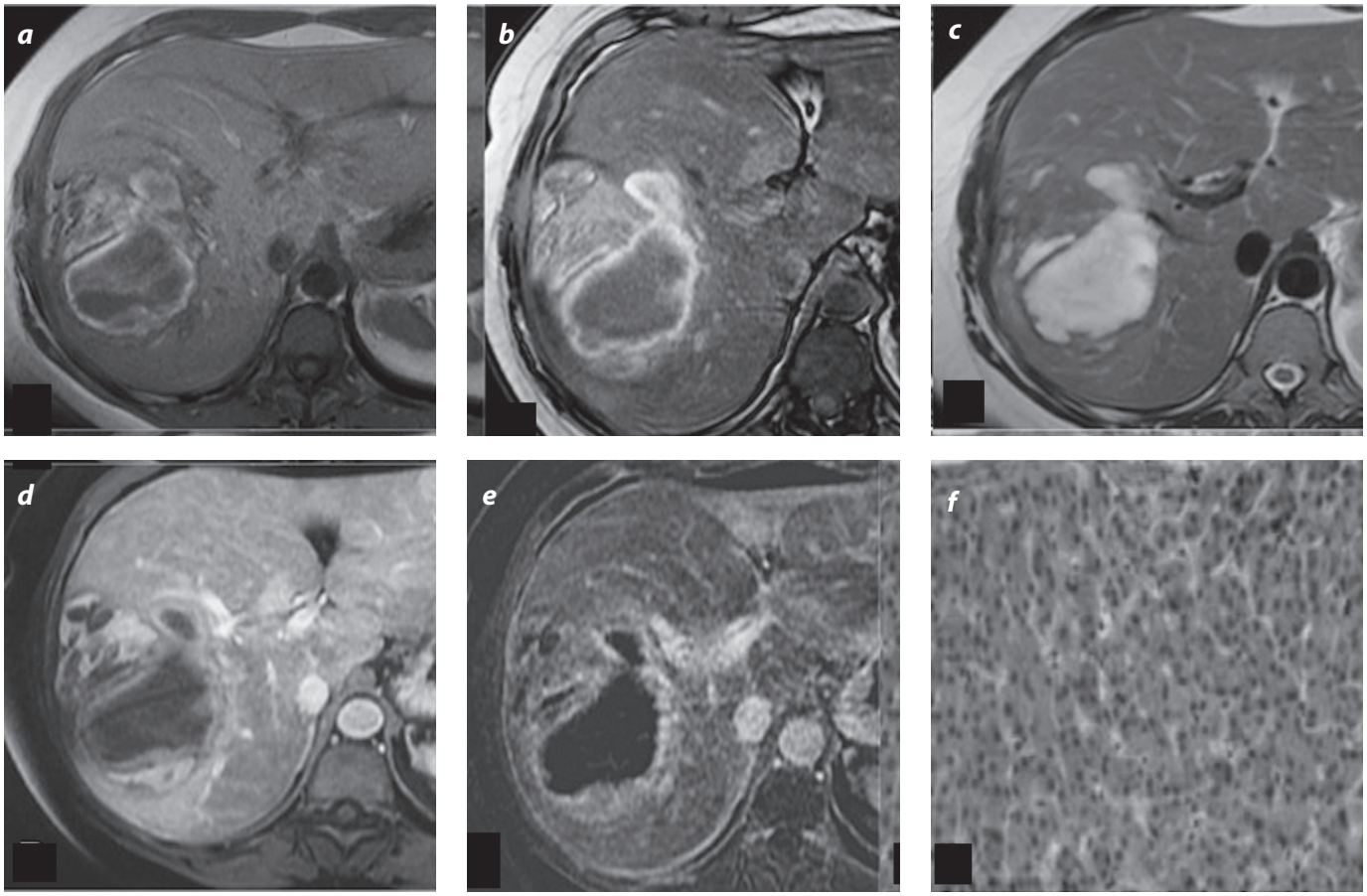

Figure 2. a) Sequence with axial phased T1 information. A mass in the right hepatic lobe can be seen, with areas of high signal intensity, mainly on the periphery b) Sequence with out of phase axial T1 information. A loss of hepatic signal can be seen due to steatosis with persistence of the high signal of mass intensity, which shows a hemorrhagic component. c) Sequence with T2 information without fatty saturation, predominantly shows the mass with high signal intensity and some areas of low peripheral signal intensity due to hemorrhage. d) Sequence with T1 post gadolinium information in the arterial phase. 3) Subtraction image in the arterial phase which shows an enhancement, mainly peripheral. f) Histopathological imaging where hepatocytes distributed in a disorganized manner can be seen, separated by the sinusoids compatible with hepatocellular adenoma, inflammatory variety.

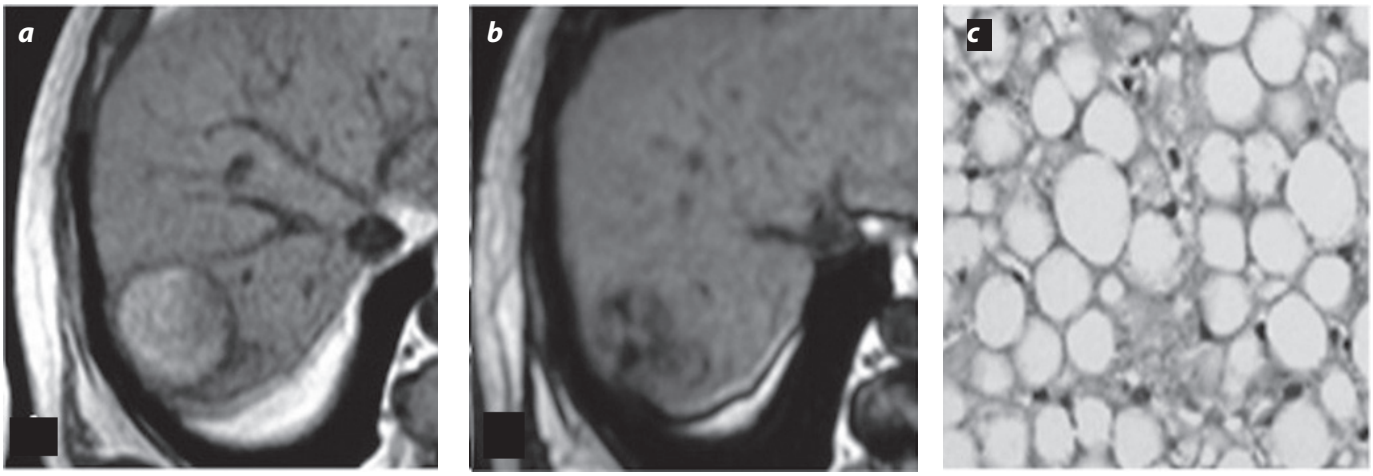

Figure 3. a) Sequence in the axial plane with phased T1 inflammation shows a rounded lesion with a high signal. B) Sequence with out of phase T1 information. A signal loss can be seen, showing a fatty component. c) Histopathology which confirmed a hepatocellular adenoma, steatosic variety.

Hepatocellular adenoma associated with the mutation of β-catenin

It corresponds to 15-18% of all AHC. They are frequently present in men, associated with their use of hormones, glycogen deposit disease (EDG) and familiar adenomatous polyposis. (2, 12, 14).

Their imaging characteristics are non-specific, they are high-intensity signal lesions with a homogenous or appearance, depending on the degree of hemorrhage or necrosis: with an intense enhancement with the contrast medium from the arterial phase, which may or may not persist in portal and tardy phases. They can simulate hepatocarcinoma focal points (2.5).

Of all the subtypes of adenomas, they are the ones which are most associated with malignant degeneration in hepatocellular carcinoma, occurring in up to 5-10% of patients (17). The main risk factors for malign transformation are: male sex, glycogen-deposit disease, use of anabolic steroids, subtype mutation β-catenin and lesions over 5 cm (17-20). Even though they are also associated with bleeding, this complication is not very frequent (2).

Unclassified hepatocellular adenomas

Menos del 10% de los AHC no expresan ninguno de estos marcadores fenotípicos, sin anormalidades específicas desde el punto de vista genético ni histopatológico. Sin patrón típico imaginológico. Se encuentran pocos datos en la literatura respecto a este subtipo (2).

Liver adenomatosis

It is a clinically different condition, infrequent, which was initially described in 1985 by Flejou (21). It has been defined as a presence of over 10 ADH which engages both lobes, without a background of glycogen deposit disease or therapy with steroids (22) (figure 4). It usually occurs in women between the fourth and fifth decades of life (23).

Its etiology is still uncertain. They have been considered as potential factors associated with hepatic vascular anomalies, mutations with the FNH gene -1α and the non-alcoholic origin hepatic fat infiltration (24,25).

Adenomatosis can be associated with any subtype of AHC, whether it is of an inflammatory variety, related to the FNH-1 α mutation or β-catenin; accordingly, its imaging characteristics will be variable (4,26,27).

Contrary to what was previously believed, this condition in itself is not associated with a greater risk of complications. The tumor subtype and size determine the risk of bleeding and malignancy (22). There are few informed cases in literature regarding malign transformation in patients with adenomatosis (6, 23, 28). The management of these patients varies according to the phenotype variety (29, 30).

Differential diagnosis

The AHC differential diagnosis of steotasic variety is established with multifocal nodular fatty infiltration, where the prominent enhancement of adenomas would help in differentiation (31).

Lesions with lipid deposits, such as hepatocarcinoma, usually with well differentiated small lesions (<1.5 cm.), with a parched deposit of fat, unlike the adenomas with more uniform fat infiltration (32). However, the differentiation between inflammatory or mixed variety adenomas and hepatocellular carcinoma focal points can be more difficult, but the associated findings of chronic hepatopathy, cirrhotic changes and the elevation of tumor markers suggest this last diagnosis (33-36).

Inflammatory adenomas can simulate focal nodular hyperplasia (HNF); however, findings in MRI studies such as a central scar, radiated septa, marked enhancement in the arterial phase, isointensity to high intensity in the portal and tardy phase suggest HNF diagnosis; while the slight arterial enhancement, with lavage in the portal and tardy phases suggest a possibility of AHC. With the use of hepatospecific contrast, an HNF enhancement is detected (figure 5), which shows an isointense to high intensity lesion related to the subjacent hepatic parenchyma (1,37-41). However, certain adenomas show a capture of these types of contrast mediums, which is a finding evidenced in the study performed by Grasioli et al. (42), mainly in patients with serious base hepatic steatosis.

Therapeutic implications

LaThe previously described classification, based on genetic, histopathological and imaging characteristics of the different subtypes of AHC enable to determine the natural history and the prognosis of these lesions, as well as define treatment or follow-up options (2). Based on the recommendations described by Bioulac-Sage et al. (3), these different therapeutic possibilities also depend on clinical symptomatology.

The most frequent clinical presentation is the incidental finding, in studies by images performed due to any other motive without referring to associated symptoms. In this case, management is based on the AHC subtype and on the imaging characteristics.

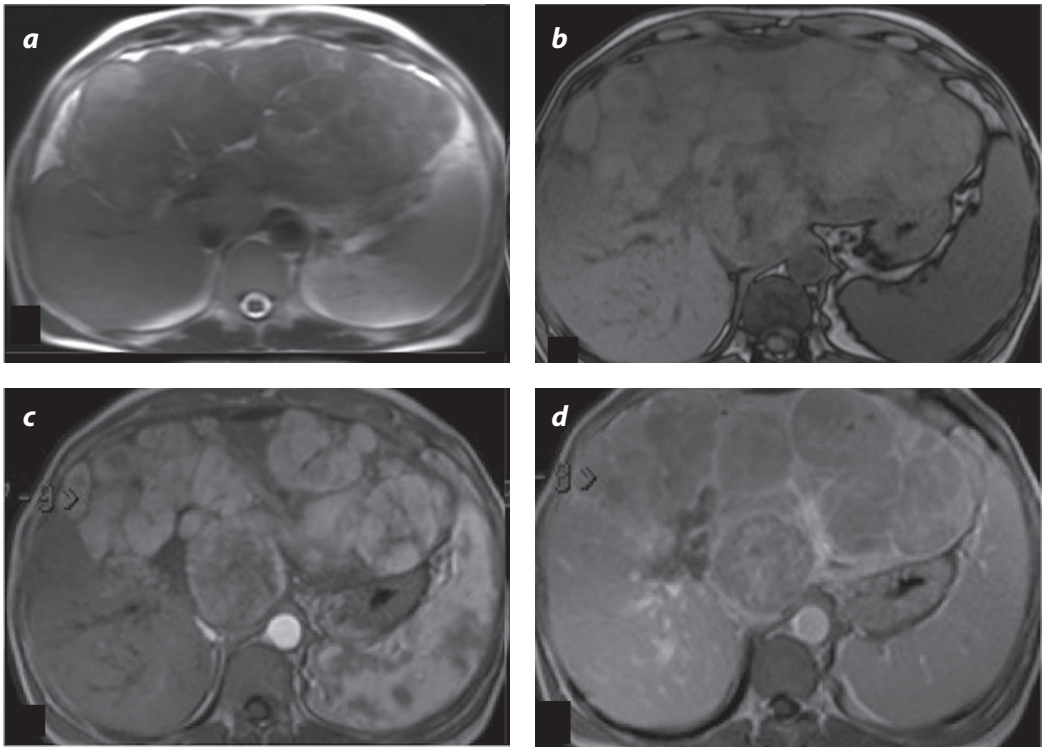

Figure 4. a) Sequence with T2 axial information without fatty saturation shows several hepatic focal lesions, which predominate in the left hepatic lobe, which mainly have an intermediate signal. b) Sequence with out of phase T2 axial information. Lesions are observed, which have an intermediate to slightly high signal. c) Sequence with posgadolinium T1 in the arterial phase show an important enhancement. d) Sequence with posgadolinium T1 in the portal phase show lavage of lesions. The histopathological confirmation showed multiple adenomatosis.

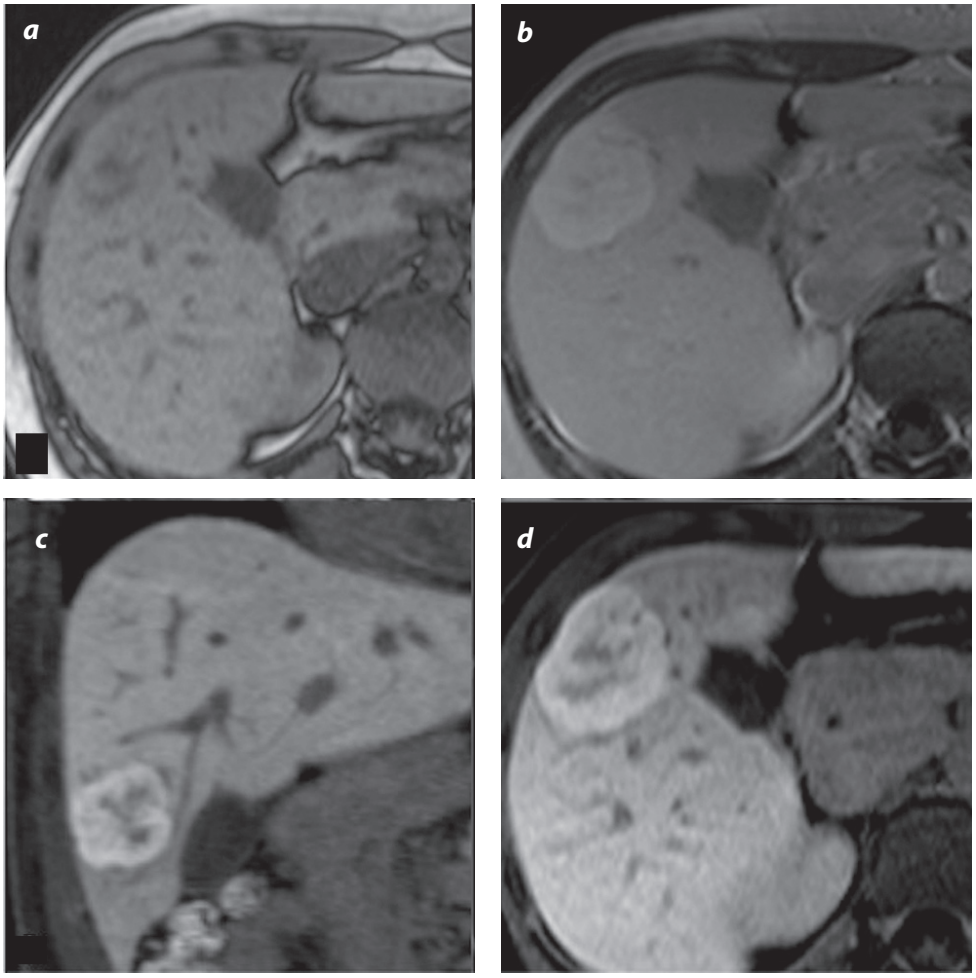

Figure 5. Magnetic resonance imaging. a) Sequence with out of phase T1 information in the axial plane. An isointense lesion is observed towards the hepatic parenchyma in segment V. b) Sequence with T1 information in post-contrast with disodium gadoxetate in the portal phase, a hypervascular lesion is shown. c) y d) Sequence with axial and coronal T1 information with fat saturation in the hepatobiliary phase. The retention of the contrast medium is observed through the lesion, demonstrating high signal intensity.

These types of patients are subdivided into AHC steatosic variety and those who do not show an intra-tumor lipid content. First of all, it is necessary to search for the etiology, such as the use of ACO, barbiturates or steroids, which must be suspended, and the imaging study must be repeated in three to six months. If the lesion is stable or its size is reduced, the patient is a candidate for follow-up without therapeutic intervention. If the size of the lesion keeps increasing despite suspending the medication, other factors such as sex and tumor size must be evaluated.

Patients with steatosic variety AHC which measures less than 5 cm will undergo genetic counseling regarding family backgrounds of adenomatosis and type 3 MODY (2,3). Patients with AHCE with intra-lesion fat content under 5 cm require a percutaneous biopsy in order to confirm if it is a subtype associated with the mutation of β-catenin. In this case, lesions will be managed surgically (2,3). Lesions in male patients, over 5 cms., or related to glycogen deposit disease must be removed (3, 47-49).

The necessary time lapse for an optimal follow up to these lesions has not yet been determined. Recommendations which suggest an annual follow-up have been found in literature (50).

As definitive treatment options different from surgery, a possibility of ablation through radiofrequency (RF), as well as hepatic arterial embolization, have been established. Ablation through RF is indicated in tumors under 4 cm., in patients who are not candidates for surgery and in patients who prefer to avoid surgery (24, 51). Lesions which grow over 5 cm in maximum diameter are candidates for any type of definitive management option. (2, 3).

Treatment of symptomatic patients depends on the duration and type of associated symptoms. Patients who suffer from hemodynamically unstable AHC rupture and patients with lesions over 5 cms., require immediate surgical treatment or embolization (52, 53). If the patient is hemodynamically stable, he/she is susceptible to conservative management (28). Patients who show persistent symptomatology, with growing lesions or lesions which maximum diameter is greater than 5 cms., must be remitted to any definitive management option (figure 6) (2,3).

Conclusions

Hepatocellular adenomas constitute a heterogeneous group of hepatic neoplasia lesions with different genetic, molecular, clinical, and imaging characteristics which enable to determine the natural history and prognosis of these lesions.

They have been classified into four main molecular subtypes: FNH-1α mutation, characterized by intra-lesion fat, constitutes the lowest risk. The other subtypes are non-statosic, including inflammatory adenoma-with greater risk of bleeding-and adenoma associated with β-catenin mutation-this last mutation has a greater risk of malignancy. The unclassified subtype does not present molecular, histological, or imaging-specific characteristics.

MRI evaluation provides a better characterization of adenomas; the study of choice is its initial classification, which, added to the clinical data of the patient, define the need for a biopsy, surgical treatment or follow-up.

Patients with AHC with less than 5 cm with steotasic variety should undergo imaging follow-up, while patients with AHC without intralesion fat content require a percutaneous biopsy in order to confirm if it is a subtype related to the mutation of β-catenin; in this case, these lesions will be surgically managed. Likewise, in male patients, or patients who suffer from glycogen deposit disease should undergo surgical resection of the lesions due to the risk of β-catenin mutation.

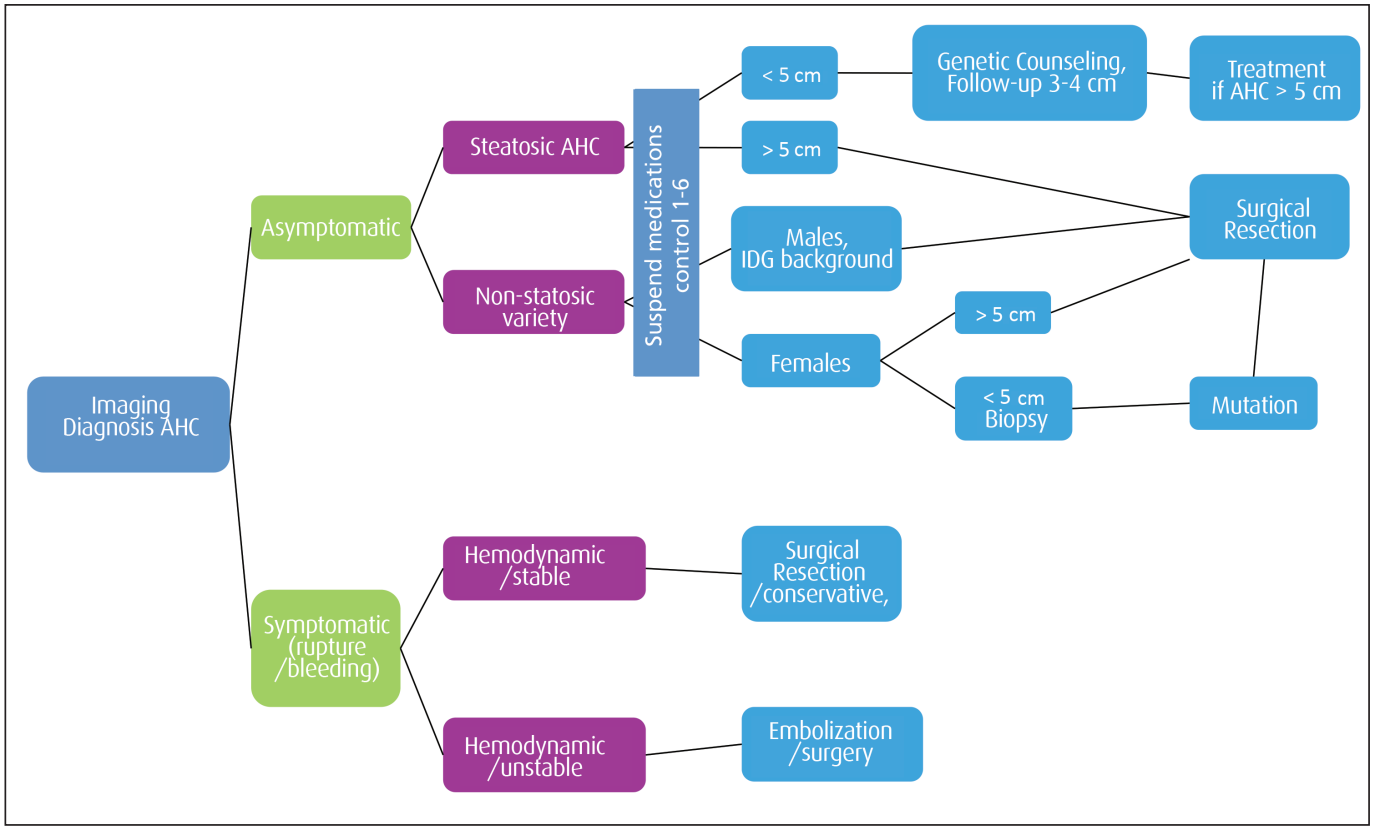

Figure 6. Imaging diagnosis

Knowledge of the different subtypes of hepatocellular adenoma and of its main clinical and imaging characteristics will enable a better management of these patients.

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