Challenging liver lesions in noncirrhotic patients: Report of three cases

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Abstract: We describe three cases of liver lesions, characterized by a discrepancy between presurgical imaging and histological features, in which the final histological diagnosis was quite different from what the surgeons expected. We present (1) a case of primary liver angiomyolipoma associated with focal nodular hyperplasia, (2) a case of perivascular epithelioid cell tumor, and (3) a case of liver splenosis associated with focal nodular hyperplasia. In all cases, a presurgical diagnosis of hepatocellular adenoma was made. Due to nonspecific clinical and radiological features, these rare liver lesions are often presurgically misdiagnosed, especially in young noncirrhotic patients. The association among different lesions represents one additional diagnostic challenge.

Keywords: Angiomyolipoma, focal nodular hyperplasia, histopathology, perivascular epithelioid cell tumor, splenosis

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Introduction

We present three very peculiar cases of liver lesions that recently came to our Pathology Unit. The three patients came with a radiological diagnosis of 'likely hepatocellular adenoma' from nonreferral centers, but the final histological diagnosis encompassed different primary lesions, whose rarity and lack of typical imaging features have made it difficult to identify them pre-operatively.

Epithelioid angiomyolipoma (EAML) is a mesenchymal neoplasm most frequently observed in the kidney, with the liver representing the most common extrarenal location.[1] The imaging features of EAML are not typical and can be misleading according to the variable amount of intratumoral fat tissue, leading to a diagnosis of lipid-rich hepatocellular carcinoma (HCC) or hepatocellular adenoma (HCA).[2–4]

Perivascular epithelioid cell tumors (PEComas) of the liver are even rarer, and they are considered by some authors as a variant of angiomyolipoma (AML), but without fat tissue: also in this case, some imaging features – such as arterial enhancement and rapid attenuation in the portal phase – can be confused with HCC.[5,6]

Splenic heterotopic tissue can be found as a consequence of a splenic trauma or surgery. The imaging characteristics of heterotopic splenic tissue in the liver vary considerably from case to case, with a wide spectrum of differential diagnoses.[7,8] In general, this diagnosis should be suspected when a well-circumscribed subcapsular nodule with enhancement in the arterial phase is seen in a patient with a history of spleen traumatism.

With the present report, we focus on the actual difficulties represented by these rare cases in the daily practice. The discrepancy between pre-operatory diagnosis and histological picture can complicate the pathologist's diagnostic management; especially if the surgeon doubts the benign nature of the lesion during the macroscopic examination, he is likely to ask for a frozen-section analysis (even more complex). An interesting and challenging feature of this series is the association of a common benign liver lesion with these more difficult lesions, as we found in two out of three cases.

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Materials and methods

The three patients were free from chronic liver disease or cirrhosis, and received a pre-operatory radiological diagnosis of 'likely hepatocellular adenoma' in nonreferral centers for primary liver lesions. Therefore, they were addressed to our Institution for liver resection. Due to the benign nature of the lesions, radiology was not repeated, and in one case, the atypical features of the lesion drove the surgeons to ask for a frozen-section analysis. In the other cases, frozen-section analysis was not required, but the final histopathological report was quite different from what has been expected. Approval from ethics committee was not required for the present cases, because they were deemed not to constitute research at our Institution. However, written informed consent was obtained from the three patients.

Surgical material was sent to our Pathology Unit, and formalin-fixed, embedded in paraffin, and routinely processed for histological diagnosis. For diagnostic purposes, 2-μm-thick sections were cut from each paraffin block for hematoxylin–eosin and reticulin stains, as well as for immunohistochemical (IHC) analysis. IHC was automatically performed by means of Benchmark ULTRA® immunostainer following the manufacturer's instructions (Ventana – Roche, Ventana Medical Systems, Oro Valley, AZ, USA). According to the different cases, the following antibodies were used: HMB45 (mouse monoclonal, clone HMB45), MART-1 (mouse monoclonal, clone A103), α-SMA (alpha-smooth muscle actin; mouse monoclonal, clone 1A4), glutamine synthetase (GS; mouse monoclonal, clone GS-6), and Ki-67 (rabbit monoclonal, clone 30-9).

Case description

Case 1

A 39-year-old woman with a prolonged history of oral contraceptives underwent abdominal ultrasound (US) and computed tomography (CT) due to a raise in aminotransferases and gamma glutamyl transpeptidase (γGT). The serum levels included: aspartate aminotransferase (ALT) 187 U/L (normal level < 35 U/L), alanine aminotransferase (AST) 171 U/L (normal level < 35 U/L), γGT 58 U/L (normal level < 38 U/L), alkaline phosphatase (AP) 96 U/L (range 30–120 U/L),

and total bilirubin 0.48 mg/dL (normal level < 1.20 mg/dL). CT revealed a 11-cm lesion occupying the whole left liver lobe, partially exophytic, characterized by inhomogeneous enhancement in arterial phase and rapid wash out in portal phase, and showing areas of adipose tissue. These findings suggested HCA (Figure 1(b)). Multiple lesions of the right lobe coexisted, characterized by hypervascularization in arterial phase and rapid portal wash-out. A left lobectomy – with intraoperatory biopsy of one lesion of the right lobe – was performed. During surgery, the surgeon found that the lesion of the left lobe was macroscopically atypical in color and consistency, not suggesting HCA. So, the left hemihepatectomy performed was sent for frozen-section analysis.

The surgical specimen presented a large red-purple solid area, with yellowish nodular areas and two distinct nodules of grayish compact tissue and a central scar (Figure 1(a)). At histology, the red-purple area showed a heterogeneous morphology, and it constituted epithelioid cells – not resembling hepatocytes in morphology – without mitosis or necrosis, and with abnormal vascularity. The grayish lesions were composed of multiple nodules of hepatocytes without nuclear atypia, arranged in trabeculae or nests with fibrous septa and a central stellate scar. The frozen-section diagnosis was 'foci of FNH in the context of non-hepatocellular epithelioid tumor, to be defined on permanent section'. On definitive slides, some areas of the red-purple lesion were characterized by dystrophic vascular structures, with a tortuous pathway, epithelioid cells with abundant eosinophilic cytoplasm, and nuclei with prominent nucleoli (Figure 1(c)), mixed to mature adipose tissue and areas of smooth muscle tissue, with a distinct leiomyoma-like nodule (of 1.4 cm; Figure 1(d)). At IHC tumor, cells were diffusely positive for HMB45 and MART-1,[9,10] and the muscle component for α-SMA. The two focal nodular hyperplasia (FNH) were positive for GS with a map-like pattern and negative for HMB45 (Figure 1(e)). The tissue obtained from the biopsy of the lesion of the right lobe showed the same morphological and IHC features, and a diagnosis of FNH was made as well.

Based on the morphology and IHC findings, the final diagnosis was 'epithelioid angiomyolipoma (EAML), associated with focal nodular hyperplasia (FNH)'.
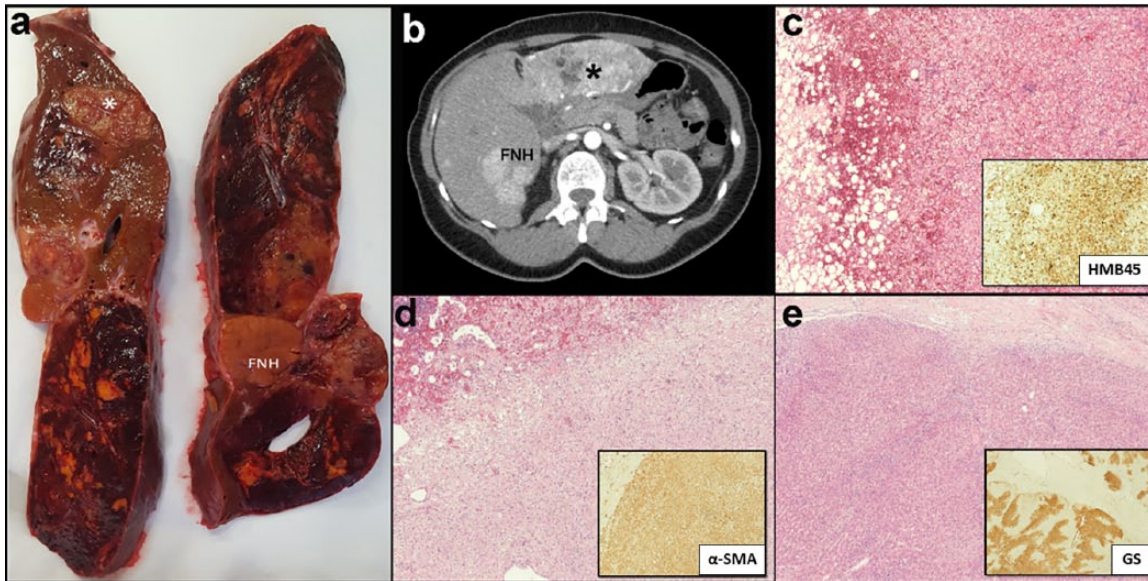
Figure 1. Case 1: (a) macroscopic appearance of EAML occupying the left liver lobe, with distinct nodules of FNH and leiomyoma (asterisk); (b) computed tomography appearance of EAML (asterisk) and FNH foci of the right lobe; (c) histological features of EAML [hematoxylin–eosin (H&E) stain, 4× magnification] with HMB45 immunoreaction (4× magnification); (d) a distinct leiomyoma nodule within the EAML (H&E stain, 4× magnification), with α-SMA immunoreaction (2× magnification); and (e) histological features of FNH (H&E stain, 4× magnification) with 'map-like pattern' GS immunoreactivity (2× magnification).
EAML, epithelioid angiomyolipoma; GS, glutamine synthetase; FNH, focal nodular hyperplasia; SMA, smooth muscle actin.

Case 2

A 32-year-old woman with a history of nonHodgkin lymphoma during childhood (treated with radiotherapy and chemotherapy when she was 2 years old) underwent abdominal US for a raise in aminotransferase levels during follow-up; US revealed a lesion of the right hepatic lobe, compatible with HCA. The serum levels included the following: ALT 199 U/L (normal level < 35 U/L), AST 158 U/L (normal level < 35 U/L), γGT 60 U/L (normal level < 38 U/L), AP 95 U/L (range 30–120 U/L), and total bilirubin 0.92 mg/dL (normal level < 1.20 mg/dL). A magnetic resonance imaging (MRI) was therefore performed, showing a solid roundish formation with a vascularized capsule, which is hypointense in T1 and weakly hyperintense in T2; the lesion remained hypointense in delayed sequences. The conclusion was suspected HCA, needing histological confirmation. A surgical resection of the lesion was performed, encompassing VI and VII liver segments, of 13.5 cm in dimensions. Grossly, the lesion was made of grayish solid tissue occupying almost the whole specimen, with mixed infiltrative or expansive margins. At histology, the lesion constituted epithelioid cells and spindle cells with marked atypia, very low mitotic index, scattered mature adipocytes, and a rich vascularization (Figure 2(a)–(d)). At IHC, tumor cells were diffusely immunoreactive for HMB45,[11,12] with occasional spindle cells positive for α-SMA and low proliferative index or Ki-67 (Figure 2(b) and (c)).

Based on the morphology and IHC findings, the diagnosis was 'epithelioid angiomyolipoma with prevalent pericytic/perivascular epithelioid cell component (EAML/PEComa)'. Focally infiltrative margins, size, presence of mitosis (albeit rare), and epithelioid morphology suggested an uncertain malignant potential.[11]

Case 3

A 46-year-old male with a history of previous splenectomy for trauma, experienced an episode of urinary hemorrhage. The serum levels included the following: ALT 16 U/L (normal level < 35 U/L), AST 14 U/L (normal level < 35 U/L), γGT 40 U/L (normal level < 38 U/L), AP 43 U/L (range 30–120 U/L), and total bilirubin 0.72 mg/dL (normal level < 1.20 mg/dL). Abdominal US was performed, and multiple liver nodules were incidentally found. MRI confirmed the presence of multiple liver lesions (the biggest of 2.6 cm), characterized by enhancement in arterial phase and wash out in portal or delayed
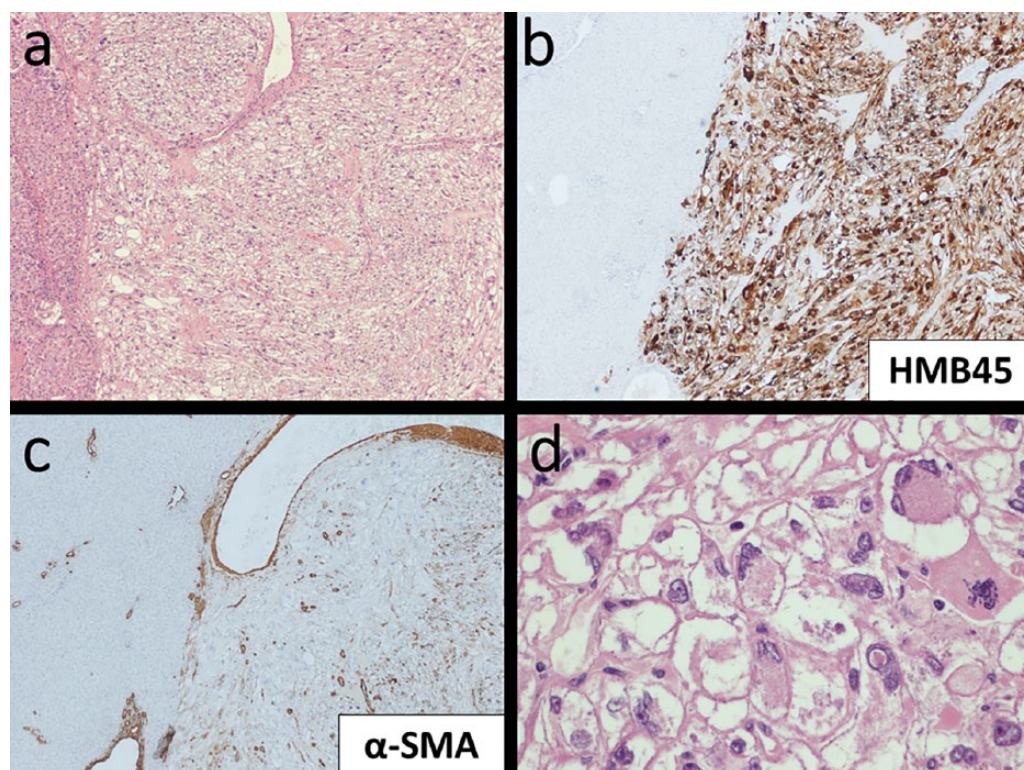
Figure 2. Case 2: (a) PEComa: epithelioid cells and spindle cells in a solid and nested architecture, with scattered mature adipocytes and a rich vascularization (H&E stain, 4×); tumor cells are diffusely positive for HMB45 (b) with scant cells positive for α-SMA (c). (d) A detailed picture at higher magnification (40×), showing the marker cell atypia.
H&E, hematoxylin–eosin; PEComa, perivascular epithelioid cell tumor; SMA, smooth muscle actin.

phase, without evident signal reduction in sequence T1, compatible with nonsteatotic or noninflammatory adenomas (with recommendation of histological confirmation) (Figure 3(a)). Only one lesion (of 4.4 cm) showed a central scar and enhancement in arterial and portal or delayed phase, with inhomogeneous hyperintensity in hepatobiliary phase, compatible with FNH (Figure 3(c)). Eight surgical wedge resections were performed with intraoperatory US. The liver wedges were sent to our Pathology Unit: seven out of eight lesions were small well-circumscribed, red-purple nodules, and the eighth lesion was made of grayish compact tissue with a central scar. At histological evaluation, the red-purple nodules constituted mature ectopic splenic tissue, with a normal red pulp largely composed of cordal macrophages and a poorly formed lymphocytic white pulp (Figure 3(b)). The single grayish lesion showed morphological features and GS immunoreactivity diagnostic of FNH (Figure 3(d)).

Based on the morphology and IHC findings, the diagnosis was 'hepatic splenosis with associated FNH'.

Discussion

We described here three cases of primary liver lesions, characterized by a discrepancy between presurgical imaging and histological features. EAML and PEComa are two very rare primary liver tumors, instead splenosis is more commonly seen, especially after spleen surgery. Nevertheless, pre-operatory imaging diagnoses were 'hepatocellular benign lesions' (namely, HCA) in all cases. The radiological criteria for the diagnosis of HCC are well-defined,[13,14] especially in cirrhotic patients, whereas the diagnosis of these rare liver tumors in noncirrhotic patients is more difficult due to the lack of 'typical' imaging markers. For example, a recent work on 23 hepatic AML (the largest published so far) showed that most of them are diagnosed as HCC on imaging, due to the presence of hyperintensity in arterial phase, and that the highest diagnostic accuracy of pre-operatory imaging is 23%.[15] The other radiological features are largely dependent on the amount of adipose tissue in the tumor, which is very variable.
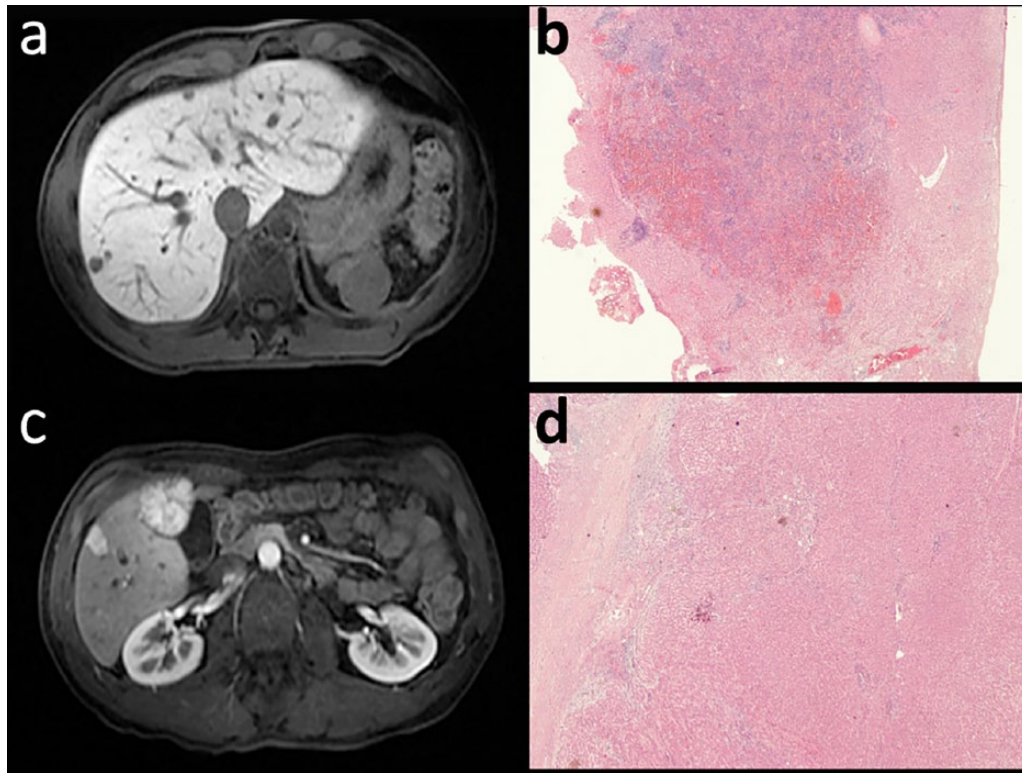
Figure 3. Case 3: (a) magnetic resonance imaging of the multiple liver lesions; (b) histological appearance of a focus of mature ectopic splenic tissue (H&E stain, 2×); and (c) imaging and (d) histological picture of the associated FNH (H&E stain, 2×).
FNH, focal nodular hyperplasia; H&E, hematoxylin–eosin.

One interesting feature of our series is the association of hepatic splenosis (case 3) and EAML (case 1) with FNH. In case 3, it is easy to hypothesize a coincidental association, because heterotopic splenic tissue is a consequence of either trauma or surgery, or both,[16,17] in a liver with a pre-existing FNH. The association with EAML is more intriguing: EAML is a vascular neoplasia, and FNH is thought to occur as a response to a vascular injury, with ensuing disorganized growth of hepatocytes and bile ducts.[18] The only similar case described in the literature is the association between an AML and an FNH in a child who underwent radiotherapy for pelvic rhabdomyosarcoma.[19] In this case, the lesions were spatially separated, whereas in our case 1, two FNH were found within the EAML. Whether FNH foci are the consequence of vascular injury due to EAML, or both EAML and FNH are the result of a predisposition of the liver to develop vascular malformations and neoplasms remains unclear.

Primary liver PEComa is very rare, with slightly more than 30 cases described in the literature.[20] PEComa belongs to the same family as AML, being composed predominantly by perivascular or pericytic cells, without mature vascular, muscular, or adipose tissues. PEComas show the same diagnostic issues at radiology as AML, and the diagnosis of PEComas is even more problematic, because they are lesions of uncertain behavior.[11]

Conclusion

The presurgical diagnosis of benign liver lesions should never be underestimated, especially in young noncirrhotic patients. More imaging techniques should be used in these cases to make the correct pre-operative diagnosis, and to limit frozen-section analysis, which can be very challenging. The possible association among different lesions presents additional difficulties for radiologists and pathologists, who need to be aware of the existence of such entities and associations.[4]

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