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Hepatic angiomyolipoma: mutation analysis and immunohistochemical pitfalls in diagnosis

Zhen Yan[1], **James P Grenert**[1], **Nancy M Joseph**[1], **Chuanli Ren**[2], **Xin Chen**[3], **Nafis Shafizadeh**[4], and **Sanjay Kakar**[1]

[1]Department of Pathology, University of California, San Francisco, San Francisco, CA, USA

[2]Department of Laboratory Medicine and Cancer Institute, Northern Jiangsu People's Hospital, Clinical Medical College of Yangzhou University, Yangzhou, China

[3]Department of Bioengineering/Therapeutic Sciences, University of California, San Francisco, San Francisco, CA, USA

[4]Department of Pathology, Southern California Permanente Medical Group, Woodland Hills, CA, USA

Abstract

Aims: Hepatic angiomyolipoma (AML) often shows epithelioid morphology with inconspicuous fat. Epithelioid component can mimic hepatocellular adenoma (HCA) or carcinoma (HCC). The aims of this study were to examine the expression of commonly used markers for HCA or HCC in hepatic AML and highlight pitfalls in diagnosis.

Methods and results: Resected hepatic AMLs ($n = 16$) were reviewed; reticulin stain, immunohistochemistry for glutamine synthetase (GS), β-catenin and liver fatty acid binding protein (LFABP) were performed along with Sanger sequencing of exon 3 of *CTNNB1* and next-generation sequencing (NGS). Predominant epithelioid component (≥50%) was seen in 80% of cases. Foamy macrophage was present in 33% of cases. High-risk histological features were often present in tumours with benign outcome: marked atypia (19%), mitoses (20%) and necrosis (33%). GS staining (≥10% of tumour) was seen in epithelioid components in 13 (87%) cases, and was diffuse (>50% of tumour) in six (40%) cases. LFABP staining or nuclear β-catenin staining was not seen in any case. Sanger sequencing and NGS did not reveal *CTNNB1* mutation in any tested case. NGS demonstrated *TSC2* mutations in all five cases tested.

Conclusions: The predominance of epithelioid component resembling HCA or HCC is common in hepatic AML. Absence of LFABP and presence of fat can be mistaken for *HNF1*α-inactivated HCA. Diffuse GS staining can be mistaken for β-catenin-activated HCA or HCC. Diffuse GS expression is not related to *CTNNB1* mutation. All tested cases showed *TSC2* mutation, supporting this as the driving genetic event for hepatic AML.

Address for correspondence: Sanjay Kakar MD, Department of Pathology, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143, USA. sanjay.kakar@ ucsf.edu.

Conflicts of interest

None of the authors have any conflicts of interest with regard to this study.

Keywords

angiomyolipoma; immunohistochemistry; liver; TSC2

Introduction

Hepatic angiomyolipoma (AML) is a mesenchymal tumour that belongs to the category of perivascular epithelioid cell tumours. As opposed to the renal counterparts, most hepatic AMLs are sporadic, and only 5–15% occur as part of tuberous sclerosis complex (TSC).[1–3] Hepatic AML tends to have a prominent epithelioid morphology and can be monotypical, i.e. composed of a myoid component without mature adipose tissue and aberrant thick-walled blood vessels.[4,5] The epithelioid component can morphologically mimic hepatocellular neoplasms such as hepatocellular adenoma (HCA) or hepatocellular carcinoma (HCC), leading to erroneous diagnosis, particularly in needle biopsies.[5,6] AMLs also closely resemble HCC on imaging.[7,8] The distinction is important, as the vast majority of AMLs behave in a benign fashion, and reports of recurrence or metastasis are rare.[9–14]

We have observed anecdotal cases of AML which were mistaken for hepatocellular neoplasms on haematoxylin and eosin (H&E) stain, and in which immunohistochemical markers such as liver fatty acid binding protein (LFABP) and glutamine synthetase (GS) had been obtained. These cases showed negative LFABP leading to the suspicion of hepatocyte nuclear factor alpha (HNF1α)-inactivated HCA, while diffuse GS staining has led to suspicion of β-catenin-activated HCA/HCC.[15] This led us to examine a series of hepatic AMLs focusing on immunohistochemical markers used commonly in HCA and/or HCC. We also explored the molecular basis of diffuse GS staining.

Material and methods

CASE SELECTION

The study group comprised 16 resected cases of hepatic AML, nine of which were resected at the University of California San Francisco (UCSF) between 2000 and 2017, and seven cases from the Southern California Permanente Medical Group between 2003 and 2016. Clinical information and outcome data were obtained by review of the electronic medical record. The slides were reviewed to confirm the diagnosis in all cases. The study was approved by the Committee on Human Research at University of California San Francisco (CHR no. 10–04369; status current), which was recognised as the Institutional Review Board for this study by the Southern California Permanente Medical Group. The requirement of informed consent was waived as part of the study approval.

IMMUNOHISTOCHEMISTRY

Immunohistochemistry for LFABP, GS, β-catenin, CD68 and CD117 was performed on 5-μm-thick sections from formalin-fixed, paraffin-embedded blocks (Table 1). In brief, sections were dewaxed in xylene, heated in citrate buffer, blocked for endogenous peroxidase by 0.3% hydrogen peroxide, blocked further for endogenous avidin and biotin and incubated with the primary antibody. The streptavidin–biotin–peroxidase method with

diaminobenzidine hydrochloride as the chromogen was used for detection. The sections were then dehydrated and cover-slipped. GS staining was recorded as diffuse when moderate to strong cytoplasmic staining was present in >50% of tumour cells, and patchy when moderate to strong cytoplasmic staining was present in 10–50% of tumour cells. All other results were regarded as negative. Diffuse staining was categorised further as diffuse homogeneous and diffuse heterogeneous (moderate to strong cytoplasmic staining in >90% and 50–90% of tumour cells, respectively).

SEQUENCING OF EXON3 OF CATENIN BETA 1 (*CTNNB1*) GENE

Genomic DNA was extracted from 10-μm sections obtained from paraffin-embedded blocks. Conventional Sanger sequencing of exon 3 of *CTNNB1* was performed in three cases.

NEXT - GENERATION SEQUENCING (NGS)

In five AML cases, capture-based NGS was performed at the UCSF Clinical Cancer Genomics Laboratory (CCGL) targeting the coding regions of 479 cancer genes. Sequencing libraries were prepared from genomic DNAs extracted from both tumour and normal background tissue. Sequencing was carried out on a HiSeq 2500 System (Illumina, San Diego, CA, USA). The analysis was based on the human reference sequence UCSC build hg19 (NCBI build 37) using the following software packages: BWA (0.7.10-r789), CNVkit (0.3.3), Samtools [1.1 (using htslib 1.1)], Pindel, Picard tools: 1.97 (1504), IGV, GATK (2014.4–3.3.0–0-ga3711), Nexus Copy Number, SATK (2013.1–10-gd6fa6c3), Freebayes, Annovar (v2015Mar22) and Delly. The genetic variants were classified as pathogenic/probably pathogenic for recurring activation (hot-spot) mutations in established oncogenes and truncating, splicing or recurrent mutations in known tumour suppressor genes. Mutations were classified as variant of uncertain significance (VUS) when it was not known to occur in the tumour, did not inactivate a tumour suppressor gene and/or was not found in databases such as COSMIC or BioPortal.

Results

CLINICOPATHOLOGICAL FEATURES

The age range at the time of diagnosis was 8–78 years (median 43). There were 10 (63%) women. All cases were sporadic and there was no clinical evidence of tuberous sclerosis complex (TSC) or renal involvement. All cases except one were unifocal, ranging from 1.3 to 26 cm (median = 3.2 cm). One case had two tumour nodules (6.1 and 2.4 cm). Follow-up information was available for 10 patients with a median duration of 17.5 months and mean of 29.4 months (range = 3–108 months). One patient developed recurrence in the liver along with involvement of inferior vena cava and diaphragm as well as lung metastasis 9 years after resection. The remaining eight patients were alive with no evidence of recurrence or metastasis at last available follow-up. One patient was an organ donor who died in a motor vehicle accident and the tumour was resected as part of the evaluation of the liver for transplant.

HISTOPATHOLOGICAL FEATURES

Predominance of the epithelioid component (≥50% of the tumour) was seen in 12 (80%) cases, while three (19%) tumours had a greater than 80% proportion of epithelioid cells (Figure 1A). The epithelioid cells were arranged in sheets, and were polygonal with moderate to abundant eosinophilic granular or pale cytoplasm, indistinct cell membrane, eccentric vesicular to hyperchromatic nuclei and variably prominent nucleoli. The fat component was predominant (>50%) in two (13%) cases, while it was 10% or less in six (39%) cases. Marked cytological atypia was seen in three (19%), mitoses >1 in 50 high-power fields in three (20%) and necrosis in five (33%) cases (Figure 2). Three tumours were large (>5 cm) and had necrosis, all of which had benign outcome (follow-up period 60–69 months). One case with malignant outcome was 15 cm with 70% epithelioid component, moderate cytological atypia, necrosis and no significant mitotic activity. Foamy cell collections were present in five (33%) cases (Figure 3). Reticulin stain was available in four cases, and showed a reticulin-poor stroma in all cases (Figure 1B).

IMMUNOHISTOCHEMISTRY

HMB-45 (Figure 4A) and smooth muscle actin (Figure 4B) were positive while S-100 was negative in all 16 cases, confirming the diagnosis of AML (Table 2). Immunohistochemistry for β-catenin revealed membranous staining without nuclear labelling in all eight cases that were examined. Moderate to strong GS staining in ≥10% of tumour cells was noted in 13 (81%) cases, and in >50% of tumour cells in six (38%) cases (Figure 5). Of the latter, four were diffuse homogeneous and two were diffuse heterogeneous. LFABP and CD117 was negative in all eight cases in which it was performed (Figure 6). CD68 staining highlighted clusters of foamy macrophages in five (31%) tumours, while the tumour cells were CD68-negative.

SEQUENCING OF *CTNNB1* GENE

To explore the possibility of *CTNNB1* (β-catenin) mutation as an explanation for diffuse GS staining, Sanger sequencing of exon 3 of *CTNNB1* was performed in three cases, two with diffuse staining and one with patchy GS staining. No mutations were detected in any case.

NGS

NGS analysis was performed in five cases, two with diffuse and three with patchy GS staining. Somatic mutations in the *TSC2* gene were identified in all five cases (transcript ID NM_000548), including bi-allelic mutations in four cases (Table 3). No other pathogenic or probably pathogenic mutations were identified in any case. One case in an 8-year-old boy showed monoallelic *TSC* mutation, along with three additional mutations that were classified as variants of uncertain significance (VUS): *SPRY2* p.S139Y, *ERBB4* p.L1296M, *KMT2D* p.A4679S. Germline mutations in *TSC1* or *TSC2* were not present in any of the five cases. Mutations in the *CTNNB1* gene or other genes involved in Wnt signalling pathway, such as *APC* and *AXIN*, were not encountered. There were no definite copy number alterations; however, the tumour content was low in some cases, which precluded an accurate assessment of the copy number data.

Discussion

Hepatic AML is often composed predominantly or entirely of an epithelioid myoid component that can closely mimic hepatocellular neoplasms such as HCA and HCC. On imaging, the enhancement in AML is similar to HCC leading to an erroneous radiological diagnosis in most cases.[5,7,16] All AML cases were sporadic in this study. Although nearly half renal AMLs occur in association with tuberous sclerosis, this association is seen in only 5–15% in hepatic cases.[1–3] There is no standard definition of an epithelioid AML, but a cut-off of 80% epithelioid component has been proposed for renal AML.[17,18] Based on this criterion, <5% of renal AMLs are epithelioid. Epithelioid component is seen more commonly in its hepatic counterpart and comprised nearly 20% of AMLs in our series. Other studies have also reported that hepatic AMLs tend to be epithelioid and monotypical.[5,19,20] The combination of epithelioid morphology, absent or inconspicuous fatty/vascular components and reticulin-poor stroma can be misinterpreted as HCC. Helpful pointers to AML include the lack of distinct cell outlines, which gives a ‘flowing’ appearance to the tumour. Foamy macrophage clusters were seen in one-third of the cases, which can be useful for diagnosis.

The criteria of malignancy in AMLs are not well established. Aggressive features described in renal AMLs-include older age, large size, epithelioid variant, severe atypia, high mitoses, necrosis, lymphovascular invasion and renal vein invasion extra-renal extension,[21,22] but are not reliable.[17,23] Size >5 cm and mitoses ≥1 in 50 high-power fields were the only features that predicted malignant behaviour in one large study.[24] A three-tier approach was advocated by Folpe *et al.*, with division into benign (fewer than two high-risk features), malignant (greater than or equal to two high-risk features) and uncertain malignant potential (tumours with nuclear pleomorphism or size >5 cm, but no other high-risk features).[25] The seven high-risk features in this study included size >5 cm, high nuclear grade, hypercellularity, mitotic rate of >1/50 high-power field, necrosis, infiltration into surrounding normal parenchyma and vascular invasion. Most reported cases of malignant hepatic AML in the literature had at least two high-risk features, with most being >5 cm and having necrosis,[4,9,11,26] including one case in the current study. Additional high-risk features such as marked nuclear atypia (three cases), high mitoses (two cases) and vascular invasion (two cases) were described in other reports of malignant hepatic AML.[10,27,28] Two reported cases with malignant outcome would have been considered as AML with uncertain malignant potential based on the Folpe criteria, as they were >5 cm but did not have other high-risk features.[12,29] However, the reliability of these criteria is uncertain, as many hepatic AMLs with benign outcome also show similar features. In our series, AMLs with benign outcome also showed high-risk histological features, including five (33%) with size >5 cm, three (20%) with mitoses >1 in 50-high power fields and five (33%) with necrosis. Three cases with benign outcome had two high-risk features (large size and necrosis). Similar findings have been reported in the literature, with two or more high-risk features observed in AMLs with benign outcome.[30–32] Vascular invasion has often been noted in AMLs with benign outcome.[33,34] The lack of CD117 expression was postulated as a feature of malignancy based on one case;[10] however, CD117 was negative in all eight cases in our series with benign outcome.

If the morphological features of AML are mistaken for a hepatocellular neoplasm, it can lead to work-up with immunohistochemical stains such as LFABP and GS. All hepatic AMLs tested in our series were negative for LFABP by immunohistochemistry. As LFABP is a protein that is found normally in hepatocytes, the negative result in AML is expected. Among hepatocellular tumours, loss of LFABP occurs typically as a result of *HNF1*a mutation, and is used for the diagnosis of *HNF1*α-inactivated HCA.[35] The combination of epithelioid morphology and negative LFABP in AML can be mistaken for *HNF1*α-inactivated HCA or HCC.

Diffuse positive GS staining was observed in 40% of cases, and can raise the possibility of β-catenin-activated HCA or HCC. Diffuse GS staining in most hepatocellular neoplasms is related to activation of the Wnt-signalling pathway, due most commonly to mutations in exon 3 of *CTNNB1* and less commonly to mutations in *APC* and *AXIN* genes. This leads to translocation of β-catenin into the nucleus and subsequent transcription of genes involved in proliferation, differentiation, cell growth and development.[36] In our series, nuclear β-catenin was not seen by immunohistochemistry in AML, and mutations in *CTNNB1* were not identified by Sanger sequencing (exon 3) or NGS in any of the tested cases. Similarly, there were no mutations by NGS in the other Wnt-signalling pathway genes, such as *APC* and *AXIN*, to explain the diffuse GS staining.

TSC1/TSC2-encoded proteins (hamartin and tuberin) modulate cell functions through the mTOR signalling, and also regulate cell growth and proliferation. Germline mutations in *TSC1* or *TSC2* are observed in AMLs occurring in tuberous sclerosis, while *TSC2* mutations have been described in sporadic renal AMLs.[37,38] Mutational analysis by sequencing has not been reported in sporadic hepatic AMLs, but loss of heterozygosity (LOH) at the *TSC2* site has been described.[1,20,39] All five tested cases of hepatic AML in our series showed *TSC2* gene mutations, with bi-allelic mutations in four cases. Based on our series, as well as reported results in the literature,[37,38] the *TSC2* mutation is perhaps a universal finding in sporadic AMLs and is probably sufficient for tumorigenesis, as other genetic events are rare. *TSC2* mutations are scattered throughout the gene and mutations in 40 of 41 exons have been reported.[40] Exons 34–38 that encode for the GAP-region with GTPase activity are often involved (two cases in this series), and mutations in exon 10 can interfere with binding with TSC1 protein (one case in our series).[40]

TSC1 and TSC2 proteins may also be involved in regulating the Wnt-signalling pathway. It has been shown that the TSC1/TSC2 complex may bind to GSK3 and axin to promote β-catenin degradation and therefore prevent its nuclear translocation and inhibit Wnt-stimulated TCF/LEF-dependent transcription.[41,42] Hence, the *TSC1*/*TSC2* mutation in AML may up-regulate the expression of GS by its effect on the Wnt signalling pathway without involving *CTTNB1* mutation. It is also possible that *TSC1/TSC2* mutations may induce GS expression in hepatic AML independently of Wnt. Additional studies are necessary to evaluate activation of the Wnt signalling pathway in hepatic AML.

In summary, the predominance of epithelioid component and inconspicuous fat in most hepatic AMLs can be mistaken for hepatocellular adenoma and HCC. Absence of liver fatty acid binding protein (LFABP) and presence of fat can be mistaken for HNF1α-inactivated

hepatocellular adenoma, while diffuse GS and can be mistaken for β-catenin-activated hepatocellular adenoma or HCC. Foamy macrophage clusters may be useful to raise the possibility of AML. Adverse histological features do not predict malignant behaviour reliably. *TSC2* mutations are present in all hepatic AMLs.

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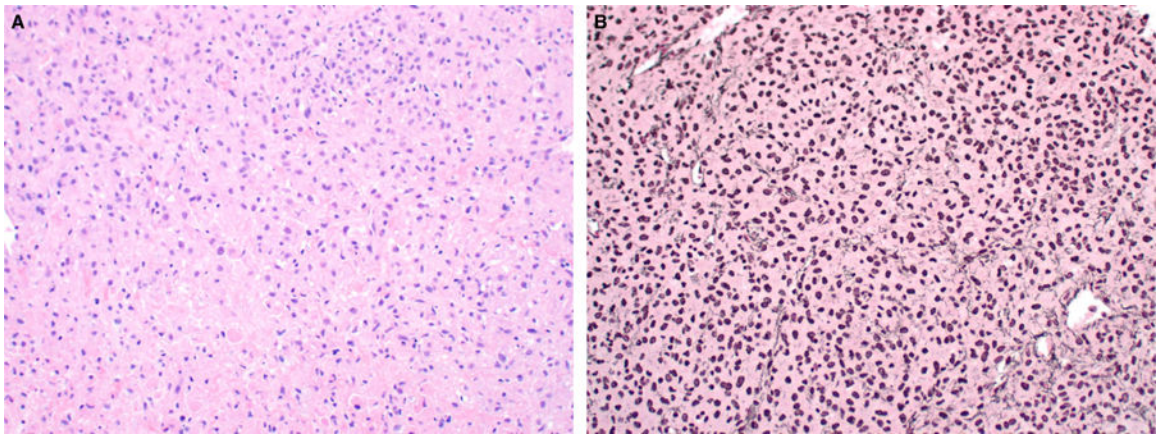

Figure 1.

Hepatic epithelioid angiomyolipoma lacking fat (**A**, haematoxylin and eosin stain) and showing a reticulin-poor stroma (**B**, reticulin stain). These findings can mimic hepatocellular adenoma or hepatocellular carcinoma.

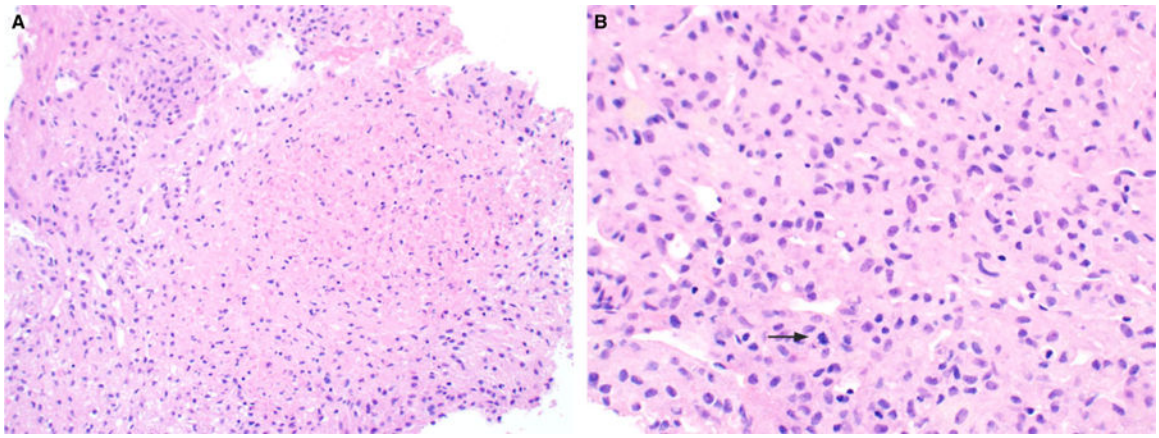

Figure 2.

Necrosis [**A**, haematoxylin and eosin (H&E) stain] and mitosis (**B**, H&E stain) have been described as criteria for malignant hepatic epithelioid hepatic angiomyolipoma, but are often also present in tumours with benign outcome. [Colour figure can be viewed at wileyonlinelibrary.com]

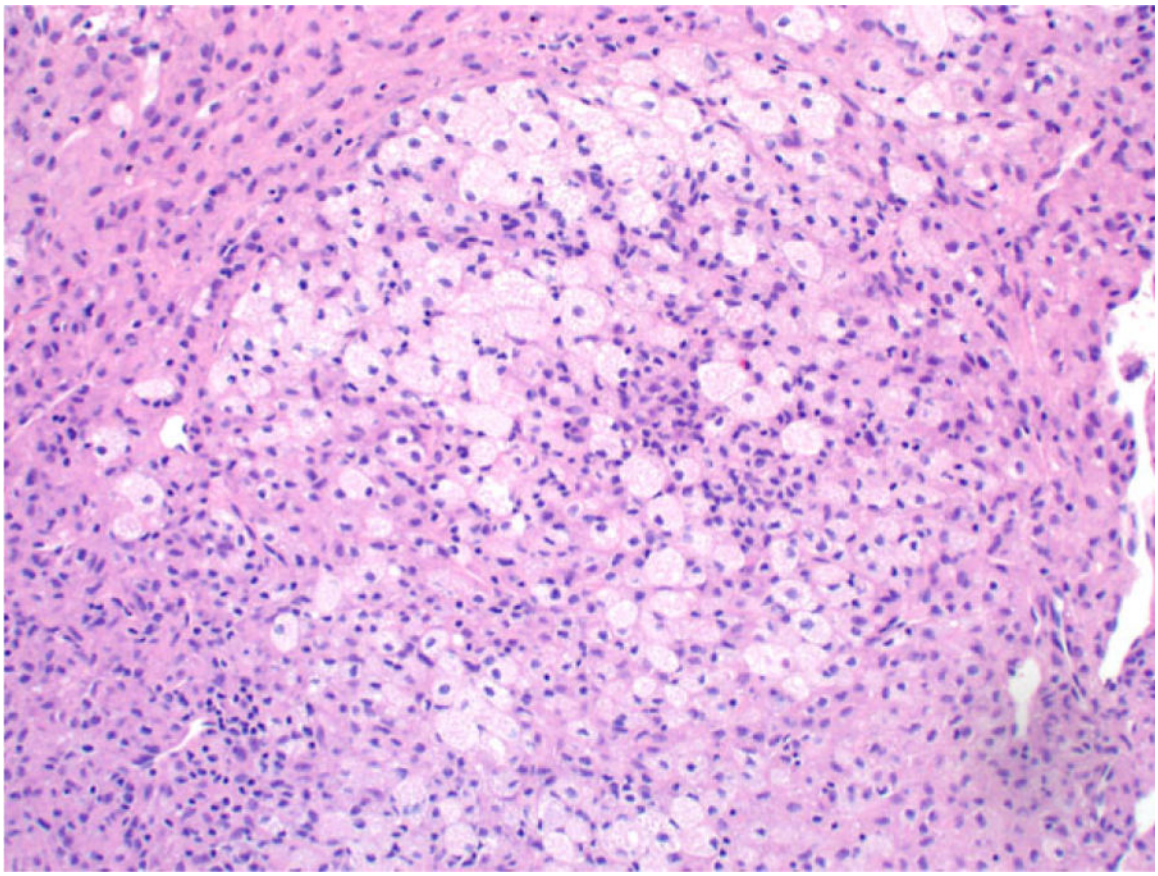

Figure 3.
Clusters of foamy macrophages can help in the diagnosis of hepatic angiomyolipoma (haematoxylin and eosin stain). [Colour figure can be viewed at wileyonlinelibrary.com]

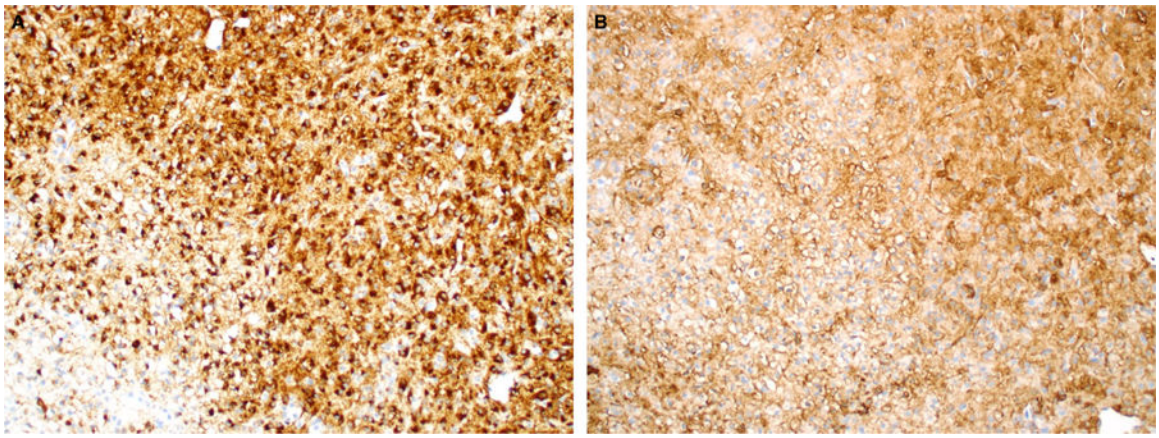

Figure 4.

Immunohistochemistry for HMB45 (**A**) and smooth muscle actin (**B**) was positive in all cases, confirming hepatic angiomyolipoma. [Colour figure can be viewed at wileyonlinelibrary.com]

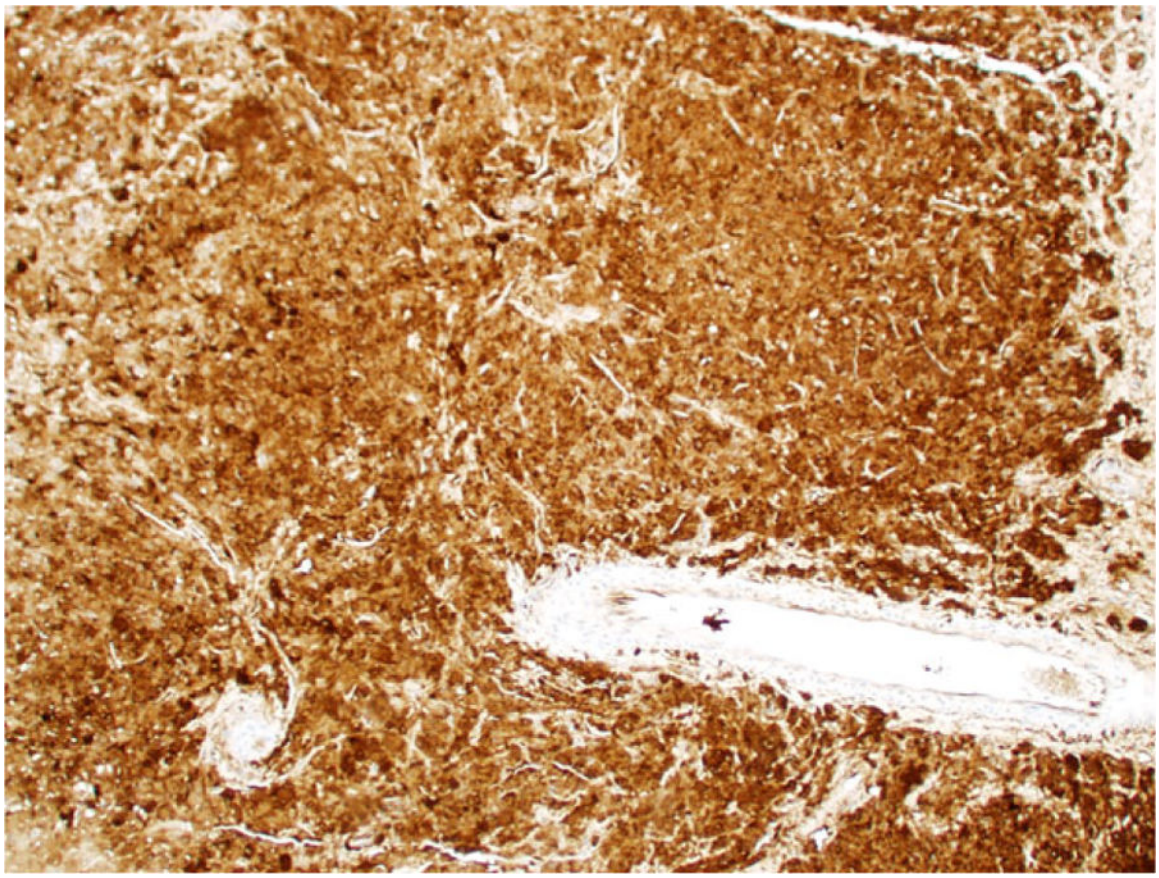

Figure 5.
Diffuse staining with glutamine synthetase (GS) can be mistaken for β-catenin-activated hepatocellular adenoma or hepatocellular carcinoma.

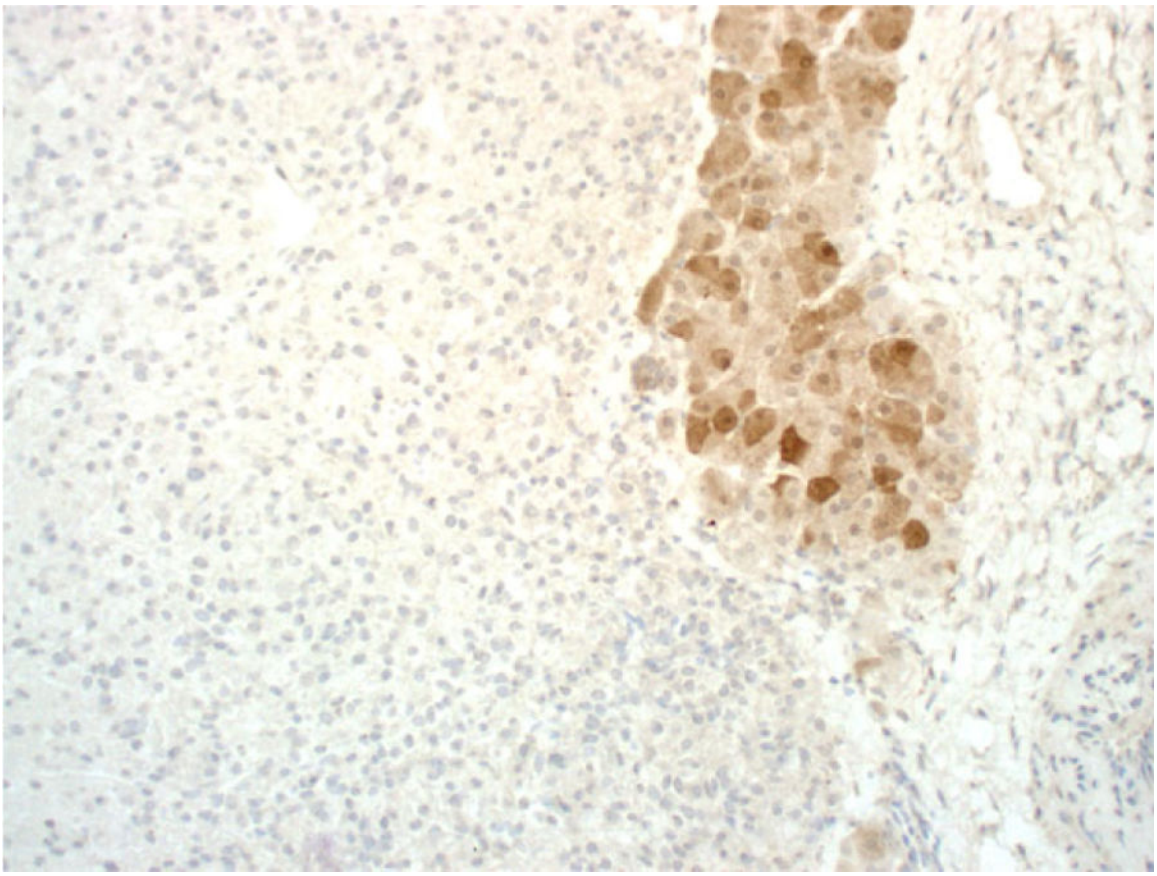

Figure 6.
Negative results with immunohistochemistry for liver fatty acid binding protein (LFABP) can mimic *HNF1*α-inactivated hepatocellular adenoma or hepatocellular carcinoma without LFABP expression. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1.

Antibodies used in the study for immunohistochemical stains

Antibodies	Vendor	Clone	Dilution	Antigen (Ag) retrieval technique
Actin, alpha smooth muscle (SMA)	Leica	Alpha sm-1	Predilute	No Ag retrieval (BOND)
CD68	Leica	514H12	Predilute	ER 2 20′ (BOND)
CD117	Dako	c-kit, CD117	1:200	ER 1 20′ (BOND)
Glutamine synthetase (GS)	Chemicon	GS-6	NA	ER 1 10′ (BOND)
HMB45	Enzo	HMB45	Predilute	ER 1 20′ (BOND)
Liver fatty acid binding protein (LFABP)	Abcam	Rabbit polyclonal	1:50	ER 1 30′ (BOND)

NA, not available.

Table 2.

Immunohistochemical results in hepatic angiomyolipoma

Stain	Result	Comment
LFABP	Negative in all 8 cases (100%)	Can be mistaken for *HNF1*α-inactivated HCA
Glutamine synthetase	Positive (≥10%): 13 (82%) Diffuse positive (>50%): 6 (38%) *	Suggests β-catenin activation, can be mistaken for HCA or HCC
β-catenin	No nuclear staining in any case (0/16)	Does not support b-catenin mutation
HMB45	Positive in all 16 cases (100%)	Supports diagnosis of AML
SMA	Positive in 15/16 (94%)	Supports diagnosis of AML
S-100	Negative in all 16 cases (100%)	Supports diagnosis of AML

LFABP, liver fatty acid binding protein; SMA, smooth muscle actin; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; AML, angiomyolipoma.

* Diffuse positive cases are included in the positive cases.

Table 3.

Mutational profile in five angiomyolipomas based on next-generation sequencing

Age/Gender	Histological type	GS staining	Somatic *TSC2* mutations	Comments
34/F	Monotypical, predominantly epithelioid	Diffuse	TSC2 c.3562delC, exon 30 (p.P1188fs) TSC2 c.2382dupG, exon 22 (p.Q794fs)	Bi-allelic frameshift mutations
48/F	Monotypical, predominantly epithelioid	Patchy	TSC2 c.4663–1G>C, exon 37 TSC2 c.2099A>G, exon 20 (p.E700G)	Bi-allelic splice site and point mutations
36/F	Triphasic; 40% epithelioid component	Patchy	TSC2 c.2355 + 1G>A, exon 21 TSC2 c.2098G>C, exon 20 (p.E700Q)	Bi-allelic splice site and point mutations
50/F	Triphasic; 50% epithelioid component	Diffuse	TSC2 c.4933dupT, exon 38 (p.D1644fs) TSC2 c.316A>T, exon 4 (p.K106*)	Bi-allelic point and nonsense mutations
8/M	Monotypical, predominantly epithelioid	Patchy	TSC2 c.849–1G>T, exon 10	Monoallelic splice site mutation