HHS Public Access

Author manuscript

Hum Pathol. Author manuscript; available in PMC 2017 January 18.

Published in final edited form as:

Hum Pathol. 2016 August ; 54: 143–151. doi:10.1016/j.humpath.2016.03.018.

Hepatic small vessel neoplasm, a rare infiltrative vascular neoplasm of uncertain malignant potential☆,,☆☆

Ryan M. Gill, MD, PhD[a,*], **Benjamin Buelow, MD, PhD**[a], **Cheryl Mather, MD**[a], **Nancy M. Joseph, MD, PhD**[a], **Venancio Alves, MD, PhD**[b], **Elizabeth M. Brunt, MD**[c], **Ta-Chiang Liu, MD, PhD**[c], **Hala Makhlouf, MD**[d], **Celia Marginean, MD**[e], **ILKe Nalbantoglu, MD**[c], **Christine Sempoux, MD, PhD**[f], **Dale C. Snover, MD**[g,h], **Swan N. Thung, MD**[i], **Matthew M. Yeh, MD, PhD**[j], and **Linda D. Ferrell, MD**[a]

[a]University of California, San Francisco, Department of Pathology, San Francisco, California, United States, 94143

[b]Universidade de Sao Paulo, Department of Pathology, Sao Paulo, Brazil, 05508-090

[c]Washington University, Department of Pathology and Immunology, St Louis, MO, United States, 63110

[d]NCI, NIH, Rockville, MD, United States, 20850

[e]Ottawa Hospital, Department of Pathology, Ottawa, Ontario, Canada, K1H 8L6

[f]Institut Universitaire de Pathologie, CHUV, Lausanne, Switzerland, CH-1011

[g]Fairview Southdale Hospital, Edina, MN, 55435

[h]Department of Laboratory Medicine and Pathology, The University of Minnesota Medical School, Minneapolis, MN, 55435

[i]Mount Sinai Health System, Department of Pathology, NY, New York, United States, 10029

[j]University. of Washington, Department of Pathology, Seattle, Washington, United States, 98195

Summary

Characteristic but rare vascular neoplasms in the adult liver composed of small vessels with an infiltrative border were collected from an international group of collaborators over a 5-year period (N = 17). These tumors were termed *hepatic small vessel neoplasm* (HSVN), and the histologic differential diagnosis was angiosarcoma (AS). The average age of patients was 54 years (range, 24–83 years). HSVN was more common in men. The average size was 2.1 cm (range, 0.2–5.5 cm). Diagnosis was aided by immunohistochemical stains for vascular lineage (CD31, CD34, FLI-1), which were uniformly positive in HSVN. Immunohistochemical stains (p53, c-Myc, GLUT-1, and

☆Competing interests: The authors declare no conflicts of interest.

☆☆Funding/Support: Research was supported by the UCSF Department of Pathology Research Endowment (San Francisco, CA) awards to R. M. G.

*Corresponding author at: Department of Pathology, University of California, San Francisco, 505 Parnassus Ave, M590, Box 0102, San Francisco, CA 94143-0102. ryan.gill@ucsf.edu (R. M. Gill).

Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.humpath.2016.03.018.

Ki-67) for possible malignant potential are suggestive of a benign/low-grade tumor. Capture-based next-generation sequencing (using an assay that targets the coding regions of more than 500 cancer genes) identified an activating hotspot *GNAQ* mutation in 2 of 3 (67%) tested samples, and one of these cases also had a hotspot mutation in *PIK3CA*. When compared with hepatic AS (n = 10) and cavernous hemangioma (n = 6), the Ki-67 proliferative index is the most helpful tool in excluding AS, which demonstrated a tumor cell proliferative index greater than 10% in all cases. Strong p53 and diffuse c-Myc staining was also significantly associated with AS but not with HSVN or cavernous hemangioma. There have been no cases with rupture/hemorrhage, disseminated intravascular coagulation, or Kasabach-Merritt syndrome. Thus far, there has been no metastasis or recurrence of HSVN, but complete resection and close clinical follow-up are recommended because the outcome remains unknown.

Keywords

Liver; Hemangioma; Angiosarcoma; Hepatic small vessel neoplasm; *GNAQ*

1. Introduction

Over the last 5 years, samples of a rare vasoformative liver tumor have been collected for evaluation. These have been seen or sent to major liver centers in consultation with the differential consideration of hepatic angiosarcoma (AS) because they have small vascular channels with an infiltrative border. Presented here are the clinical, histologic, and molecular evaluations of this rare vascular neoplasm in the adult liver. This study also investigated immunohistochemical stains (IHCs) that can be used to differentiate this small vessel–type neoplasm, which we have termed *hepatic small vessel neoplasm* (HSVN).

2. Materials and methods

2.1. Case selection

HSVN cases (N = 17) were defined morphologically as an infiltrative vasoformative neoplasm composed of small vessels without diagnostic features of cavernous hemangioma or hepatic AS; cases were identified by an international group of collaborators based on reference images of initial cases identified at the University of California, San Francisco (UCSF) by R. M. G. and L. D. F. Samples ranged from biopsy (n = 11) to partial resections (n = 3), to hepatectomies (n = 2), and to autopsy (n = 1). For comparative study, cavernous hemangioma (n = 6) and vasoformative (ie, rather than epithelioid) hepatic AS (n = 10) cases selected from UCSF Department of Pathology files (cases were selected based on original diagnosis at UCSF [verified by R. M. G. and L. D. F.] and availability of tissue for further testing), including biopsies and resections, were studied. Demographic and follow-up data were extracted from the clinical records when possible. This research was approved by the UCSF Institutional Review Board.

2.2. Immunohistochemistry

All formalin-fixed, paraffin-embedded tissue samples were routinely processed, and serial sections from representative paraffin blocks were used for hematoxylin-eosin staining and

immunohistochemistry. Immunohistochemical analysis was performed using standard techniques. Briefly, 4-μm paraffin-embedded sections were heat-treated; deparaffinized; heated in citrate buffer; blocked for endogenous peroxidase, avidin, and biotin; and incubated with antibodies for either Ki-67 (Dako, Carpinteria, CA, clone MIB-1, 1:50), p53 (Vector, Burlingame, CA, clone DO7, 1:100), CD34 (Leica, clone Buffalo Grove, IL, QB-END/10, predilute), CD31 (Leica, clone 1A10, predilute), FLI-1 (Cell Marque, Rocklin, CA, Prep Kit 20), GLUT1 (Cell Marque, polyclonal, predilute), or c-Myc (Abcam, Cambridge, United Kingdom, clone Y69, 1:50). A subset of cases was also evaluated with additional antibodies: pancytokeratin (Dako, clones AE1 and AE3, 1:100; Becton-Dickinson, Franklin Lakes, NJ, clone Cam 5.2, 1:100), HHV8 (Vector, clone 13B10 1:100), and CD8 (Leica, clone 4B11, predilute). Sections were subsequently washed and developed with the Vector ABC kit. For Ki-67, the percentage of immunoreactive tumor cells was manually determined in hotspots, with at least 200 cells counted; any intensity of nuclear staining was scored as positive. For p53, any strong nuclear staining was scored as positive. For c-Myc, only staining of >50% of tumor nuclei (ie, diffuse) was considered positive [1]. For CD34, CD31, FLI-1, and GLUT1, any degree of staining was scored as positive. Slides were reviewed by R. M. G., B. B. (c-Myc), and L. D. F.

2.3. Molecular testing

Three HSVN cases (2 resections and 1 wedge biopsy) and 2 cavernous hemangioma resections were chosen for DNA extraction and molecular analysis using the “UCSF 500 panel.” Capture-based next-generation sequencing was performed at the UCSF Clinical Cancer Genomics Laboratory using an assay that targets the coding regions of more than 500 cancer genes, including selected introns for some genes. Sequencing libraries were prepared from genomic DNAs extracted from both tumor and normal hepatic tissue. Target enrichment was performed by hybrid capture using a custom oligonucleotide library. Sequencing was performed on an Illumina HiSeq 2500. Duplicate sequencing reads were removed computationally to allow for accurate allele frequency determination and copy number calling. 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. Methods are similar to those used in testing of a recently described smaller gene panel [2].

2.4. Statistical analysis

Analyses were performed using Student t test, χ^2 test, and analysis of variance, and $P < .05$ was considered statistically significant.

3. Results

3.1. Study populations

Study population details are presented in Table 1. The average age for HSVN patients was 54 years (range, 24–83 years), and there was a marked male predominance. The average size for HSVN, as determined by imaging or gross measurements (as indicated in pathology

reports), was 2.1 cm (range, 0.2–5.5 cm). The most common HSVN clinical presentation was with an incidental/asymptomatic single liver mass on imaging for a different clinical indication. In 1 potentially symptomatic case, there was only a “mild” elevation in liver function test results (LTs), of uncertain clinical significance, so it is unclear if LT changes were due to the tumor. One patient’s hepatic tumor was considered suspicious for focal nodular hyperplasia on imaging, which led to biopsy. In another patient, HSVN was misinterpreted, on imaging, as metastatic neuroendocrine tumor, and transarterial chemoembolization (TACE) was performed (with no apparent treatment effect) before biopsy. All HSVN patients for which there was follow-up (including 6 patients with residual tumor) were alive without evidence of metastasis or recurrence (when completely resected) (Table 1), in contrast to hepatic AS, which was uniformly fatal in a short time period. Patients with resection of cavernous hemangioma were all alive up to 6 years after diagnosis, as expected.

3.2. Gross and morphologic features

Gross evaluation, after fixation, demonstrated a poorly circumscribed unencapsulated pale tan to brown hemorrhagic lesion without cystic spaces or grossly apparent vessels (Fig. 1). All cases demonstrated similar histology showing an infiltrative tumor composed of thin-walled small vascular spaces lined by flat to plump-oval (ie, hobnail-like) endothelial cells without papillary growth, hyperchromasia, multilayering, mitotic activity, nucleoli, necrosis, or nuclear irregularity/pleomorphism (Fig. 2A–D). Luminal red cells were present, and occasional cases demonstrated extramedullary hematopoiesis (Fig. 2E). Rare luminal hyaline globules and thrombosis were noted in one case. Surrounding hepatic parenchyma may demonstrate variable hepatocyte plate expansion (Fig. 2F), sometimes with focal nodular hyperplasia-like changes, to a degree that may mimic well-differentiated hepatocellular carcinoma. The infiltrative tumor border, in which tumor cells can infiltrate between hepatic plates and around portal tracts, is further highlighted with IHC for vascular markers (Fig. 3A and B). None of the cases had features of cavernous hemangioma intermixed with the small vessel tumor, and the surrounding parenchyma was otherwise unremarkable (beyond occasional variable macrovesicular steatosis) [3]. Transarterial chemoembolization was attempted on 3 of the reported cases of HSVN but with no obvious treatment effect (Fig. 4).

3.3. Immunohistochemical results

IHCs for vascular markers (CD34, CD31, and FLI-1) were uniformly and strongly positive in all cases (N = 17). Pancytokeratin, HHV8, and CD8 immunostains were negative in the initial diagnostic workup of several HSVN cases. IHCs for potential malignant behavior (GLUT-1, p53, Ki-67, and c-Myc) were performed on HSVN cases based on tissue availability (GLUT1, n = 13; p53, n = 14; Ki-67, n = 16; and c-Myc, n = 14), which show a significant difference between mean Ki-67 proliferative index for HSVN (Fig. 5A) and hepatic AS (Fig. 5B) (3.7% and 42.8%, respectively), as well as strong positive nuclear staining for p53 restricted to hepatic AS (Fig. 5C and D) (Table 2). GLUT1 and c-Myc stains were only positive in hepatic AS, but only 2 hepatic AS cases were positive for each stain (although the c-Myc result was still significantly different when compared with HSVN). Cavernous hemangioma cases showed no proliferative activity (with Ki-67 IHC) and absent

GLUT1 and p53. The Ki-67 proliferative index was a helpful discriminator between hepatic AS and HSVN; a cutoff of 10% for the diagnosis of hepatic AS resulted in 100% sensitivity and specificity for making a distinction between hepatic AS and HSVN.

3.4. Molecular results

Sequencing of 510 genes in 3 HSVN cases revealed an activating hotspot *GNAQ* mutation in 2 of 3 samples. These 2 HSVN cases had a somatic p.Q209H mutation present at 19% and 18% mutant allele frequency in the tumor, respectively. This mutation is at one of the activating hotspots in *GNAQ* and has been described as recurrently mutated in uveal melanoma [4,5] and blue nevi [4]. One of these 2 cases also demonstrated an activating hotspot mutation in *PIK3CA* (p.H1047R) at 20% mutant allele frequency. The third case did not have known activating hotspot mutations in *GNAQ* or *PIK3CA* but did have a stop-gain mutation in *AMER1* (although this was present only at 3% mutant allele frequency, so its significance is unclear) (Supplementary Table).

We also sequenced 2 cavernous hemangioma cases as controls. Neither case had *GNAQ* mutations or other pathogenic mutations. No mutations or gene amplifications in genes associated with AS (eg, *PTPRB*, *PLCG1*, *TP53*, *MYC*, *KDM6A*, or *KDR*) [6,7] were identified in either HSVN or cavernous hemangioma cases, and there was no overlap between HSVN and published tumor profiles for AS [6,8–11].

4. Discussion

Distinction between benign and malignant hepatic vascular tumors is generally straightforward. Cavernous hemangiomas are well-circumscribed benign tumors that are readily diagnosed on histologic evaluation by their characteristic large vascular spaces lined by flat uniform endothelial cells and underlying thick fibrous septa. Unlike cavernous hemangiomas, vasoformative hepatic ASs have scant stroma and can subtly infiltrate into hepatic sinusoids and separate hepatic plates (ie, a scaffolding pattern). HSVN represents a hepatic vascular tumor of uncertain malignant potential that may be mistaken for AS due to an infiltrative growth pattern but which lacks the marked cytologic atypia of some AS cases.

By molecular analysis, 2 of 3 HSVN cases had the same activating hotspot *GNAQ* mutation, which is consistent with a clonal/neoplastic proliferation. *GNAQ* hotspot mutations have previously been described as a frequently mutated gene in melanocytic neoplasms [4,5] including benign blue nevi [4] and have recently been reported in lesional tissue in the majority of patients with Sturge-Weber syndrome and port wine stains [12,13]. *GNAQ* encodes a G-protein; G-proteins generally link cell membrane receptors to intracellular signaling pathways. In 2 of 3 HSVN cases, the *GNAQ* mutation was at a hotspot in which mutations have been shown to activate the protein (p.Q209H) [4]. By contrast, the 2 sequenced cavernous hemangioma cases showed no abnormalities in *GNAQ* or genes associated with AS, supporting their classification as benign vascular proliferations. By IHC evaluation, HSVN did have a higher Ki-67 proliferative index than cavernous hemangioma, but proliferative index was still significantly lower than hepatic AS. There was proliferative index heterogeneity in AS resection specimens; thus, a low Ki-67 proliferative index does not entirely exclude AS when evaluated on a small core biopsy. On the other hand, none of

the HSVN resection cases had a proliferative index greater than 10% anywhere in the tumor, supporting consideration of proliferative index as a positive predictor of hepatic AS, in this scenario. HSVN did not show significant p53, GLUT1, or c-Myc immunostainings, which were all diffusely positive in a subset of hepatic ASs (although only p53 and c-Myc were significant discriminators in statistical analysis).

The term *small vessel hemangioma* was used in our 2012 and 2013 abstracts [14,15] to reflect an initial impression that this tumor was probably benign. Over the next 3 years, as we collected more cases, we encountered 1 patient with HSVN who also had evidence of a splenic mass (consistent with hemangioma on imaging), so although we have not encountered any examples of definite metastasis, our follow-up is limited for complete exclusion of latent metastasis/recurrence. In addition to the activating hotspot *GNAQ* mutation described above, 1 HSVN case demonstrated an activating hotspot mutation in *PIK3CA*, which is an established hotspot oncogenic mutation in numerous cancers, including breast cancer, in which it is linked to carcinogenesis and/or tumor dedifferentiation [16–18]. Given the molecular findings and limited follow-up thus far, we recommend complete resection and close clinical follow-up for all patients. Molecular profiling of additional cases is needed to fully characterize the spectrum and significance of pathogenic mutations. A limitation of our study is that only core biopsy material is available for more than half of our cases, which limits comprehensive molecular analysis of all samples. As molecular testing becomes more commonplace, we expect to obtain additional data on our clinical cases that will provide more information on the frequency of activating hotspot *GNAQ* mutations in HSVN.

Although the mechanism of disease for HSVN is poorly understood, our finding of the same activating hotspot *GNAQ* mutation in 2 of 3 cases (1 of which also demonstrates hotspot *PIK3CA* mutation) is an important first step in fully characterizing HSVN tumorigenesis and malignant potential. *GNAQ* mutation testing in other vascular tumors in the liver, soft tissue, or other organs could provide evidence for a unifying molecular alteration in a subset of vasoformative tumors. Investigation into the basic mechanisms of *GNAQ* function is needed to determine its potential role in endothelial cell biology. Ultimately, if HSVN behaves similar to cavernous hemangioma, then in addition to possible genetic factors, future investigations could explore possible associations with estrogen and autoimmune diseases, as has been described in cavernous hemangioma [19–22]. Epidemiologic study of hepatic AS has revealed associations with specific toxins and drugs (eg, arsenic, inorganic copper, anabolic steroids, polyvinyl chloride, and thorium dioxide [with remote exposures of up to 65 years reported]) [3,23,24], but most cases are idiopathic [25]. We did not find any specific toxin or drug exposure in review of HSVN patient history. *MYC* amplification has been established in some primary (non–radiation-associated) cutaneous ASs [1], and a subset of nonhepatic, sporadic ASs has abnormal p53/*TP53* [26]; we found IHC evidence to support similar changes in hepatic AS but no IHC or molecular evidence of a *MYC* or *TP53* abnormality in HSVN.

The term *anastomosing hemangioma* has been proposed to describe a group of 6 vascular neoplasms composed of anastomosing “capillary-sized” vessels in liver and gastrointestinal tract; based on the description and published images in this 2013 report [27], some of the

reported hepatic “anastomosing hemangioma” cases could have represented the same entity we have classified as HSVN. However, in the “anastomosing hemangioma” series, 50% of the liver tumors (2/4 hepatic cases) had intermixed features of cavernous hemangioma [27], which were not a feature in our series. Cavernous hemangioma may commonly have some smaller vessels at the periphery (although usually they are not as small as in HSVN), so it is not clear if these cases included in the “anastomosing hemangioma” study represent a cavernous hemangioma variant with features intermediate between cavernous hemangioma and HSVN, or a point in tumoriogenesis for all HSVN cases. In our search for HSVN cases, we encountered several cases of cavernous hemangioma with variable small vessels, but only 1 had regions that could potentially mimic HSVN on core biopsy (Fig. 6A and B). Another difference between HSVN and “anastomosing hemangioma” is the obvious infiltration into hepatic parenchyma of the former, whereas “anastomosing hemangioma” cases were described, on histologic evaluation, as sharply demarcated from surrounding liver parenchyma [27]. Similar-appearing lesions in the kidney, testes [28], and gastrointestinal tract [27] have also been termed *anastomosing hemangioma*. Thus, given the morphologic differences between hepatic “anastomosing hemangioma” and HSVN, uncertain malignant potential, and presence of the same pathogenic genetic abnormality in 2 of 3 cases of HSVN, we favor a distinct diagnosis of HSVN for infiltrative vasoformative hepatic tumors without features of cavernous hemangioma or angiosarcoma.

Interestingly, the term *capillary hemangioma* was used for classification of the first published image of a liver tumor that may represent what we have termed *HSVN* [29], although only high-power photomicrographs of the tumor were presented (along with ultrasonographic findings). This designation is not ideal for classification of a newly recognized liver tumor, as HSVN may not share clinical or molecular features with cutaneous capillary hemangioma. Other reports on “capillary hemangioma” in the liver are of uncertain significance; either no histologic images have been shown, or the published images have not demonstrated the features of HSVN [30–32].

Imaging of these tumors is inconclusive, and in our series, radiologist impressions ranged from atypical vascular tumor to neuroendocrine tumor to HCC; biopsy is clearly needed for diagnosis [31]. In one possible description of this tumor as a “capillary hemangioma” of liver, ultrasonographic evaluation was described in detail, and the tumor is reported as hypoechoic and heterogenous [29]. On contrast-enhanced ultrasonography (with perfluorobutane), the tumor strongly enhanced rapidly and was homogeneous in the arterial predominant phase (and still enhanced in the portal predominant phase but was isoechoic to liver in the postvascular phase) [29]. Nonspecific magnetic resonance imaging findings have also been reported [33]. We noted cases with significant expansion of hepatocyte plates adjacent to the vascular tumor, which has been described in hemangiomas [34], or with focal-nodular hyperplasia-like change, which could impart the impression of a hepatic nodule on imaging and which should not be confused with hepatocellular carcinoma [34].

In summary, this study describes a series of rare vasoformative hepatic neoplasms that are infiltrative and composed of small vessels, which can histologically mimic hepatic AS. This tumor has behaved in a benign fashion, but there is limited follow-up thus far, and given its infiltrative growth pattern and our molecular findings, we recommend resection and long-

term follow-up. IHC, in particular Ki-67, p53, and c-Myc, can help in distinguishing HSVN from hepatic AS on small core biopsies, and there may be roles for molecular testing in diagnosis and management; in particular, an activating hotspot *GNAQ* mutation (p.Q209H) may represent a recurrent genetic abnormality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Sarah Bowman for assistance with manuscript preparation.

References

1. Shon W, Sukov WR, Jenkins SM, Folpe AL. MYC amplification and overexpression in primary cutaneous angiosarcoma: a fluorescence in-situ hybridization and immunohistochemical study. Mod Pathol. 2014; 27:509–15. [PubMed: 24091875]
2. Shain AH, Yeh I, Kovalyshyn I, et al. The genetic evolution of melanoma from precursor lesions. N Engl J Med. 2015; 373:1926–36. [PubMed: 26559571]
3. Bioulac-Sage P, Laumonier H, Laurent C, Blanc JF, Balabaud C. Benign and malignant vascular tumors of the liver in adults. Semin Liver Dis. 2008; 28:302–14. [PubMed: 18814083]
4. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature. 2009; 457:599–602. [PubMed: 19078957]
5. Shoushtari AN, Carvajal RD. GNAQ and GNA11 mutations in uveal melanoma. Melanoma Res. 2014; 24:525–34. [PubMed: 25304237]
6. Behjati S, Tarpey PS, Sheldon H, et al. Recurrent PTPRB and PLCG1 mutations in angiosarcoma. Nat Genet. 2014; 46:376–9. [PubMed: 24633157]
7. Antonescu CR, Yoshida A, Guo T, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. Cancer Res. 2009; 69:7175–9. [PubMed: 19723655]
8. Liau JY, Tsai JH, Yang CY, et al. Alternative lengthening of telomeres phenotype in malignant vascular tumors is highly associated with loss of ATRX expression and is frequently observed in hepatic angiosarcomas. HUM PATHOL. 2015; 46:1360–6. [PubMed: 26190196]
9. Murali R, Chandramohan R, Moller I, et al. Targeted massively parallel sequencing of angiosarcomas reveals frequent activation of the mitogen activated protein kinase pathway. Oncotarget. 2015; 6:36041–52. [PubMed: 26440310]
10. Tannapfel A, Weihrauch M, Benicke M, et al. p16INK4A-alterations in primary angiosarcoma of the liver. J Hepatol. 2001; 35:62–7. [PubMed: 11495043]
11. Weihrauch M, Markwarth A, Lehnert G, Wittekind C, Wrbitzky R, Tannapfel A. Abnormalities of the ARF-p53 pathway in primary angiosarcomas of the liver. HUM PATHOL. 2002; 33:884–92. [PubMed: 12378512]
12. Nakashima M, Miyajima M, Sugano H, et al. The somatic GNAQ mutation c.548G>a (p.R183Q) is consistently found in Sturge-Weber syndrome. J Hum Genet. 2014; 59:691–3. [PubMed: 25374402]
13. Shirley MD, Tang H, Gallione CJ, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med. 2013; 368:1971–9. [PubMed: 23656586]
14. Gill RM, Alves V, Makhlouf H, Sempoux C, Thung S, Ferrell LD. Small vessel hepatic hemangioma, an atypical hemangioma variant in adult liver. Mod Pathol. 2012; 25(Supplement 2): 413A.
15. Gill RM, Sempoux C, Makhlouf H, Thung S, Amancio TT, Alves V, Ferrell LD. GLUT1 expression in adult hepatic vascular neoplasms. Mod Pathol. 2013; 26(Supplement 2):402A.

16. Koren S, Reavie L, Couto JP, et al. PIK3CA(H1047R) induces multipotency and multi-lineage mammary tumours. Nature. 2015; 525:114–8. [PubMed: 26266975]
17. Van Keymeulen A, Lee MY, Ousset M, et al. Reactivation of multipotency by oncogenic PIK3CA induces breast tumor heterogeneity. Nature. 2015; 525:119–23. [PubMed: 26266985]
18. Wolters KL, Ang D, Warrick A, Beadling C, Corless CL, Troxell ML. Frequent PIK3CA mutations in radial scars. Diagn Mol Pathol. 2013; 22:210–4. [PubMed: 24193002]
19. Massironi S, Branchi F, Rossi RE, et al. Hepatic hemangioma in celiac patients: data from a large consecutive series. Gastroenterol Res Pract. 2015; 2015:749235. 1–6. [PubMed: 25649925]
20. Berzigotti A, Frigato M, Manfredini E, et al. Liver hemangioma and vascular liver diseases in patients with systemic lupus erythematosus. World J Gastroenterol. 2011; 17:4503–8. [PubMed: 22110281]
21. Glinkova V, Shevah O, Boaz M, Levine A, Shirin H. Hepatic haemangiomas: possible association with female sex hormones. Gut. 2004; 53:1352–5. [PubMed: 15306599]
22. Takahashi K, Iida K, Okimura Y, et al. A novel mutation in the von Hippel–Lindau tumor suppressor gene identified in a Japanese family with pheochromocytoma and hepatic hemangioma. Intern Med. 2006; 45:265–9. [PubMed: 16595991]
23. Coulier B, Pierard F, Gielen I, Maldague P. Hepatic angiosarcoma occurring 65 years after thorium dioxide (Thorotrast) exposure: imaging, surgical and histopathologic findings of a historical case. JBR-BTR. 2014; 97:254–8. [PubMed: 25603638]
24. Ito Y, Kojiro M, Nakashima T, Mori T. Pathomorphologic characteristics of 102 cases of Thorotrast-related hepatocellular carcinoma, cholangiocarcinoma, and hepatic angiosarcoma. Cancer. 1988; 62:1153–62. [PubMed: 2457426]
25. Huang NC, Wann SR, Chang HT, Lin SL, Wang JS, Guo HR. Arsenic, vinyl chloride, viral hepatitis, and hepatic angiosarcoma: a hospital-based study and review of literature in Taiwan. BMC Gastroenterol. 2011; 11:142. 1–7. [PubMed: 22200164]
26. Hung J, Hiniker SM, Lucas DR, et al. Sporadic versus radiation-associated angiosarcoma: a comparative clinicopathologic and molecular analysis of 48 cases. Sarcoma. 2013; 2013:798403. 1–8. [PubMed: 24082817]
27. Lin J, Bigge J, Ulbright TM, Montgomery E. Anastomosing hemangioma of the liver and gastrointestinal tract: an unusual variant histologically mimicking angiosarcoma. Am J Surg Pathol. 2013; 37:1761–5. [PubMed: 23887160]
28. Montgomery E, Epstein JI. Anastomosing hemangioma of the genitourinary tract: a lesion mimicking angiosarcoma. Am J Surg Pathol. 2009; 33:1364–9. [PubMed: 19606014]
29. Kameda R, Kobayashi S, Makoto U, Miyagawa K, Shinichi O. A case of capillary hemangioma of the liver examined by contrast-enhanced ultrasonography with perfluorobutane (Sonazoid®). Kanzo. 2011; 52:244–50.
30. Noda T, Sasaki Y, Yamada T, et al. Adult capillary hemangioma of the liver: report of a case. Surg Today. 2005; 35:796–9. [PubMed: 16133680]
31. Abaalkhail F, Castonguay M, Driman DK, Parfitt J, Marotta P. Lobular capillary hemangioma of the liver. Hepatobiliary Pancreat Dis Int. 2009; 8:323–5. [PubMed: 19502177]
32. Scialpi M, Piscioli I, Pusiol T, Franceschetti I. Does hepatic adult capillary hemangioma exist? Surg Today. 2010; 40:92. [PubMed: 20037850]
33. Lewis S, Aljarallah B, Trivedi A, Thung SN. Magnetic resonance imaging of a small vessel hepatic hemangioma in a cirrhotic patient with histopathologic correlation. Clin Imaging. 2015; 39:702–6. [PubMed: 25748474]
34. Sasaki M, Ikeda T, Hatanaka KC, Nakanuma Y. Hyperplastic hepatocellular nodule with localized hemangiomatosis: a hither-to unrecognized type of hypervascular hepatic lesion. Hepatol Res. 2014; 44:E77–83. [PubMed: 23927680]

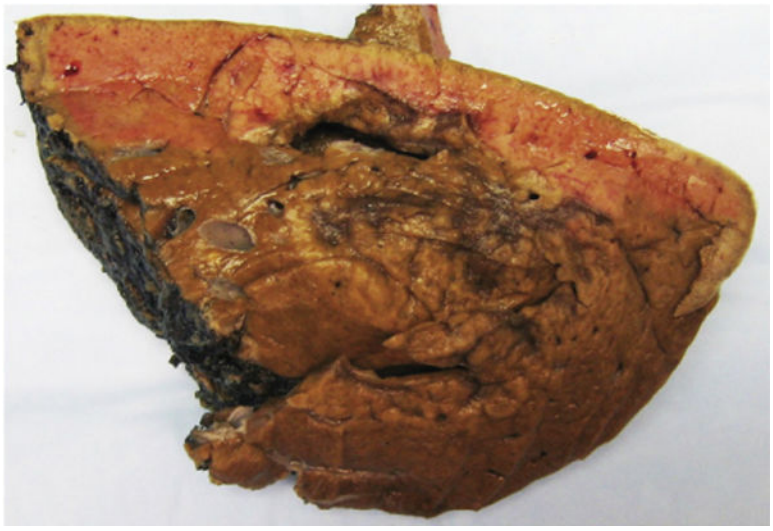

Fig. 1.

HSVN gross photograph (after fixation) demonstrates a mottled tan brown unencapsulated tumor with a poorly circumscribed border (image courtesy of Dr Gretta Jacobs, Cleveland, OH).

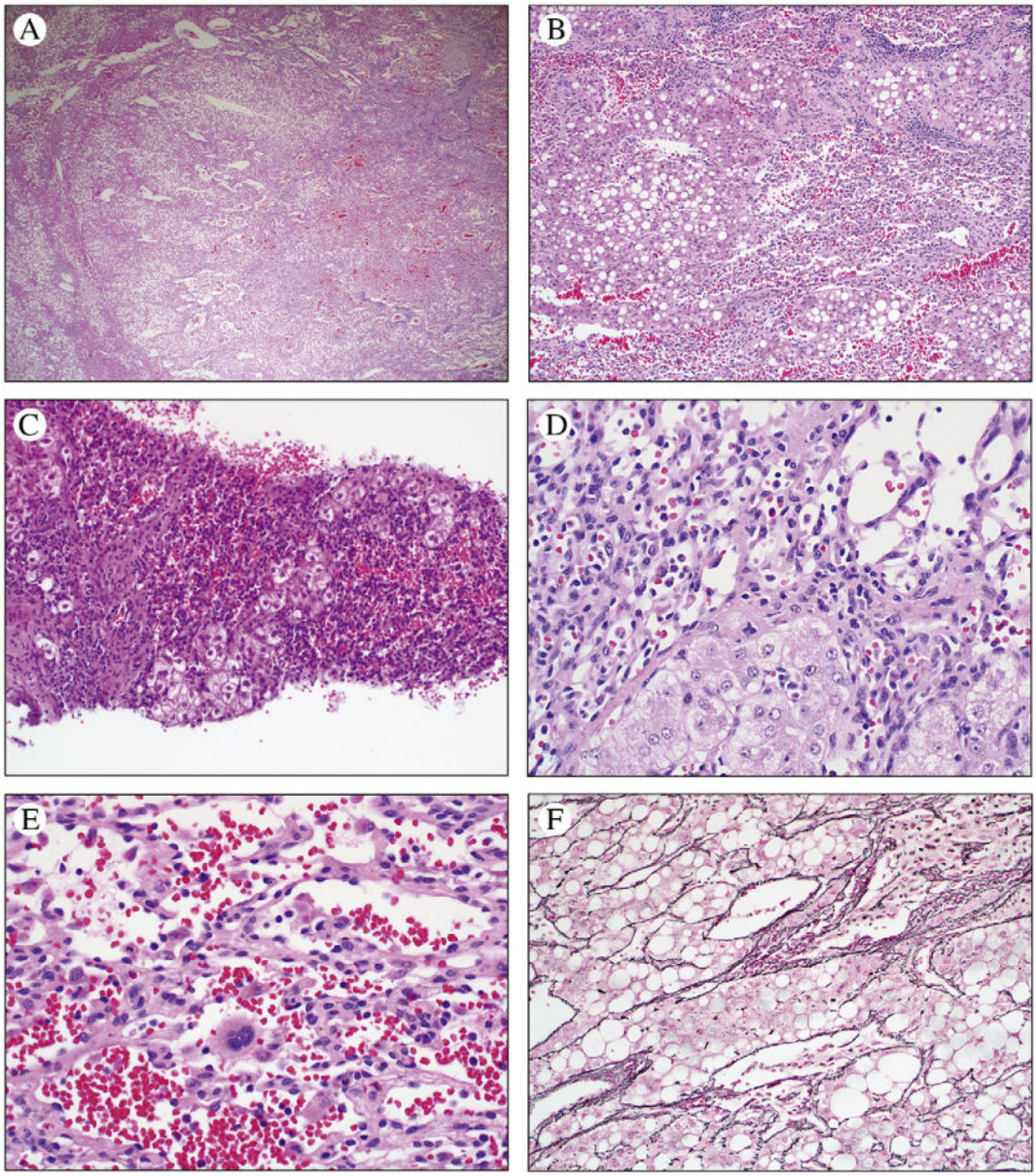

Fig. 2.

HSVN, representative images. A, HSVN composed of thin-walled small vascular spaces with an indistinct border (H&E stain, original magnification ×20). B, HSVN demonstrating extensive infiltration into sinusoids and around steatotic parenchyma (H&E stain, ×100). C, HSVN, on biopsy, with parenchymal infiltration (H&E stain, ×200). D, HSVN composed of small vessels lined by flat to plump oval tumor cells with infiltration into sinusoidal space at edge of the tumor (H&E stain, ×400). E, HSVN with extramedullary hematopoiesis (H&E stain, ×400). F, Expanded hepatic plates adjacent to HSVN (reticulin stain, ×400).

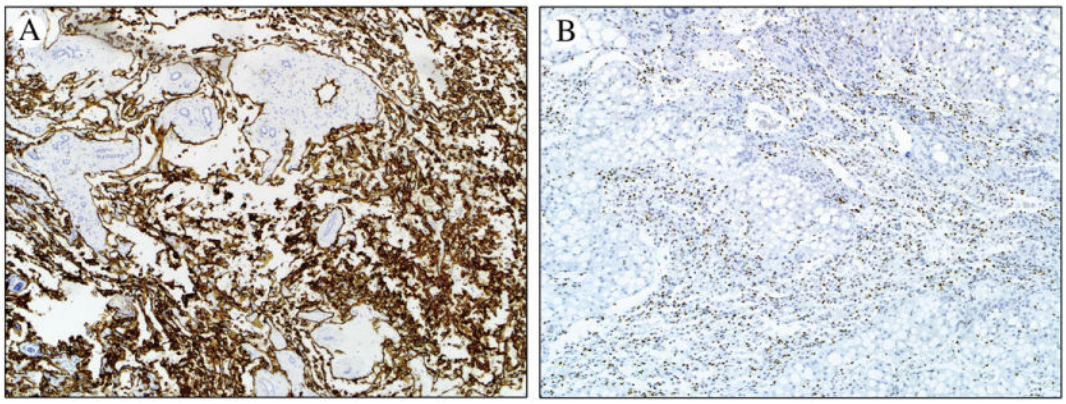

Fig. 3.

HSVN immunohistochemical staining with vascular markers. A, CD34 immunohistochemical stain demonstrates tumor infiltrating around portal tracts (×100). B, Fli-1 immunohistochemical stain highlights tumor infiltrating through fatty hepatic parenchyma (×100).

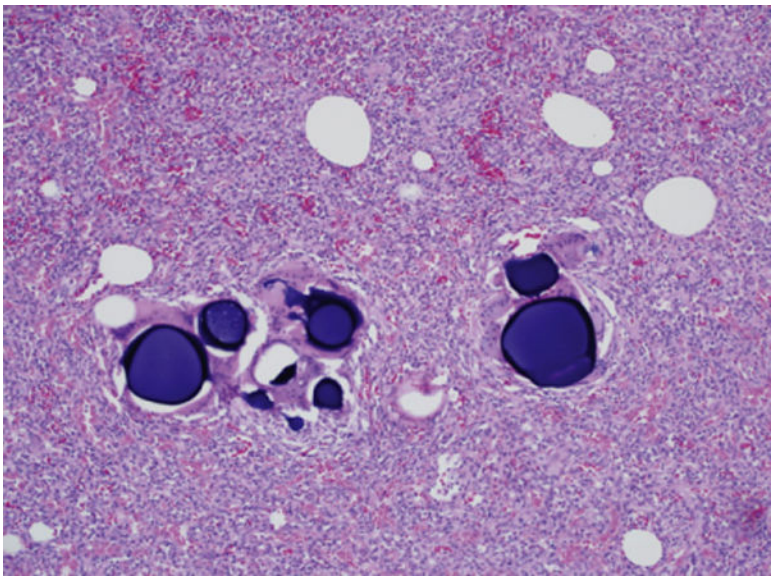

Fig. 4.
HSVN with embolization material but no evidence of treatment effect (H&E stain, ×100).

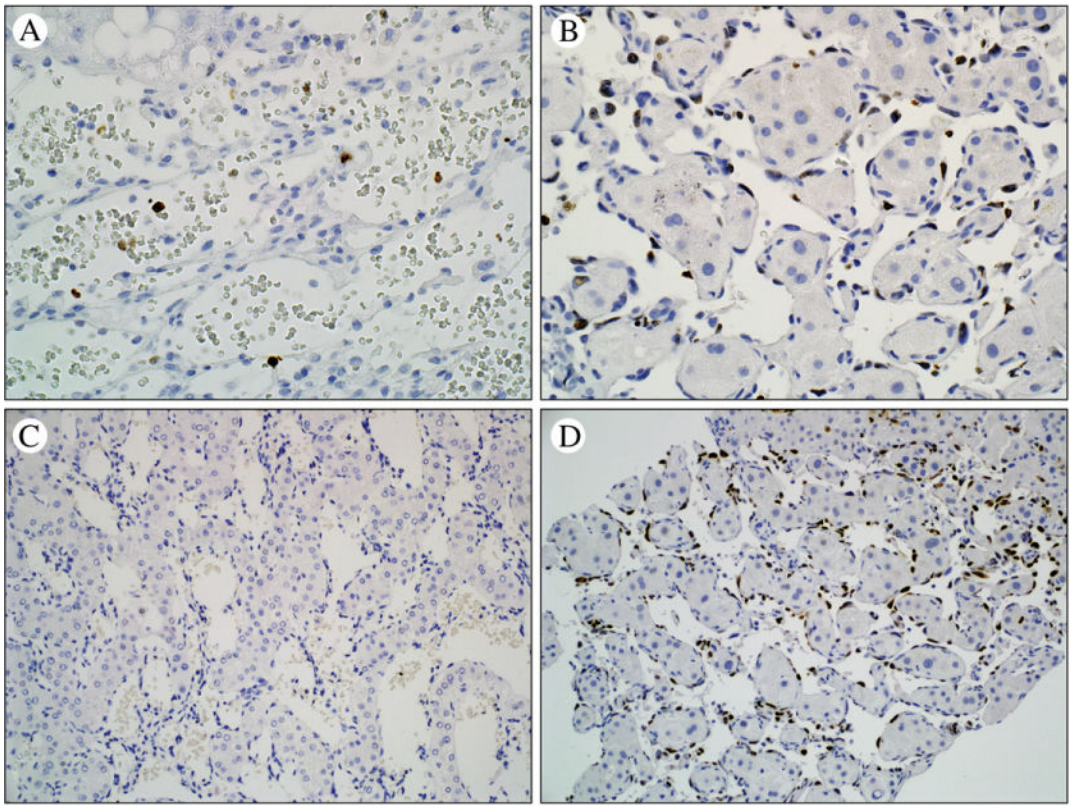

Fig. 5.

Immunohistochemical stains to distinguish HSVN from hepatic AS. A, HSVN with a low proliferative index (Ki-67 labels luminal extramedullary hematopoiesis) (Ki-67 immunohistochemical stain, ×400). B, Hepatic AS with a high proliferative index (Ki-67 immunohistochemical stain, ×400). C, HSVN with absent p53 staining (p53 immunohistochemical stain, ×200). D, Hepatic AS with strong nuclear p53 staining (p53 immunohistochemical stain, ×200).

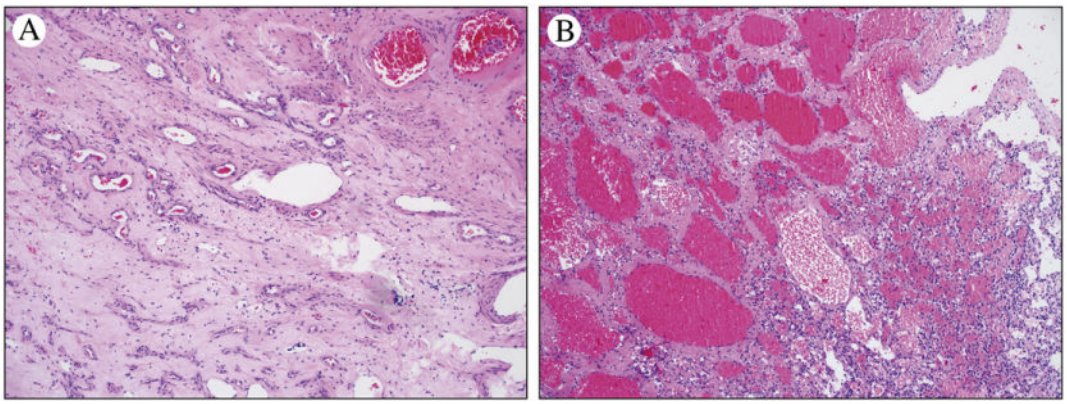

Fig. 6.

Cavernous hemangioma variants, 2 different cases (A and B) distinct from HSVN, with intermixed variably sized vessels and well-circumscribed borders (demonstrated in the lower right hand corner of [B]) (H&E stains, ×100).

Table 1

Clinical features and outcome

Case	Age (y)	Sex	Clinical history/imaging	Tumor size (cm)	Sample	Evidence of possible metastasis	Additional treatment	Outcome	Maximum follow-up (mo)
1	83	M	Incidental liver tumor	1.5	Core biopsy	No	None	ARD	5
2	58	M	HCV with a liver tumor	0.7	Core biopsy	No	Resection	ANED	12
3	57	M	Incidental liver tumor	2	Core biopsy	No	*a*	*a*	*a*
4	47	M	RCC with an incidental liver tumor	1.1	Resection	No	*a*	*a*	*a*
5	53	M	Multiple hypervascular liver tumors	2.8 (largest)	Core biopsy	No	Re-biopsy	ARD	1
6	58	F	3 incidental liver tumors at autopsy, pulmonary embolism	1.5 (largest)	Autopsy	No	*a*	*a*	*a*
7	37	F	Pregnant with an incidental liver tumor	5.5	Resection	No	None	ANED	6
8	61	M	HCV with cirrhosis and imaging suggestive of HCC	1.3	Core biopsy	No	None	ARD	1
9	43	M	NAFLD, imaging initially suggests hemangioma; 4 y later, tumor is ~50% larger and atypical for hemangioma on MRI	2.2	Resection	No	None	ANED	24[b]
10	66	M	HCV with cirrhosis and imaging suggestive of HCC	1.8	Hepatectomy	No	TACE	*a*	*a*
11	65	M	Bronchial carcinoid and imaging of liver suggestive of metastatic neuroendocrine tumor, treated by TACE, possible second 1.1-cm hepatic lesion	2.2, 1.1	Wedge biopsy	No	Radiofrequency ablation	ARD	1
12	54	M	Incidental liver tumor	4.2	Core biopsy	No	TACE followed by resection	ANED	13
13	59	F	CHF and renal failure with an incidental liver tumor	2.5	Core biopsy	No	Resection	ANED	1
14	24	F	NAFLD with resection of a 5.3-cm hepatocellular adenoma	~1	Core biopsy	No	*a*	*a*	*a*
15	67	M	Mildly elevated LT and imaging suggestive of FNH	2.7	Core biopsy	No[c]	None	ARD	3
16	77	M	Incidental liver tumor	3	Core biopsy	No	None	ARD	1
17	65	M	Alcoholic steatohepatitis with cirrhosis	0.2	Hepatectomy	No	None	ANED	12

Abbreviations: NAFLD, nonalcoholic fatty liver disease; CHF, congestive heart failure; FNH, focal nodular hyperplasia; ARD, alive with residual disease; ANED, alive with no evidence of disease.

[a] Follow-up data are not available or the category is not applicable.

[b] Twenty-four months since biopsy, 72 months since mass was detected by ultrasonography.

[c] No definite metastasis, but report of a 2.4-cm tumor with imaging features of hemangioma in spleen (not biopsied).

Table 2

Immunohistochemical stains for possible malignant potential

	HSVN	AS	HSVN *vs* AS	CH	CH *vs* AS
Proliferative index in tumor cells by Ki-67 stain, mean (range)	3.7% (0%–8%) (n = 16)	42.8% (19.8%–77.5%) (n = 10)	$P < .001^a$	0% (n = 6)	$P < .001^a$
GLUT-1	0/13	2/6	$P = .054^b$	0/6	$P = .266^b$
p53 (strong nuclear staining)	0/14	5/7	$P = .001^b$	0/6	$P = .049^b$
c-Myc (diffuse staining)	0/14	2/6	$P = .027^b$	NA	NA

Abbreviations: CH, cavernous hemangioma; NA, not applicable (testing not performed).

[a] Student *t* test.

[b] χ^2 test.