Annals of Medicine and Surgery 72 (2021) 103004

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Systematic Review / Meta-analysis

Hepatic small vessel neoplasm – A systematic review

Ian Y. Goh [a,b,*], Patricia Mulholland [a], Anna Sokolova [c], Cheng Liu [b,d,e], Mehan Siriwardhane [a]

[a] Department of General Surgery, Mater Hospital, Brisbane, Queensland, Australia
[b] Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia
[c] Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
[d] Mater Pathology, Mater Hospital, Brisbane, Queensland, Australia
[e] QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia

ARTICLE INFO

Keywords:
Neoplasia
Hepatic small vessel neoplasia
Hepatic
Liver
HSVN

ABSTRACT

Background: Hepatic small vessel neoplasm (HSVN) is a recently described vascular neoplasm of the liver that can mimic hepatic angiosarcoma (AS) because of its infiltrative nature but is considered biologically less aggressive. We carried out a systematic review of the literature after previously coming across a case of HSVN [1] to guide our surveillance.

Methods: We conducted a systematic review for all cases using PubMed, EMBASE, Cochrane Central Register of Controlled Trials, case report journals and Google Scholar according to the PRISMA guidelines using the terms "hepatic small vessel neoplasm" or "hepatic small vessel neoplasia" with no language restrictions. The review was registered with Research Registry (UIN: reviewregistry1127) [2].

Results: We identified 69 articles, of which 6 articles were eligible after screening. A total of 23 cases were identified. Median age was 58 (range 24–83 years) with a male preponderance (17 M:6F). Mean tumour size was 2.8 cm (range 0.2–15.9 cm). Mean follow-up was 7 months (range 1–24 months) with no reported evidence of recurrence in both patient groups with no residual disease or with positive margins after resection.

Discussion: HSVN appears to demonstrate a benign clinical course with no reported recurrences or metastatic disease. Long-term follow-up data will further supplement our understanding of these tumours and guide future management.

1. Introduction

Hepatic tumours can arise from epithelial or mesenchymal cells, with vascular tumours comprising the majority of mesenchymal-derived neoplasms. Vascular tumours form a spectrum that ranges from benign hemangiomas to aggressive angiosarcomas (AS), with increasing incidental detection due to widespread use of imaging modalities [3].

Cavernous haemangioma is the most common mesenchymal tumour of the liver and has a benign course. In comparison AS is aggressive, with a high recurrence rate and poor survival [4], and the median survival is only 6 months after surgery [5,6]. Hepatic small vessel neoplasm (HSVN) is a recently identified vascular neoplasm, first described by Gill et al., in 2016 [7]. This neoplasm shows features of both AS and cavernous haemangioma; despite having an infiltrative growth pattern, there is minimal cytologic atypia and mitotic activity.

Compared to hepatic AS, HSVN is believed to pursue a benign course, although its long-term malignant potential is unknown. HSVN is a rare lesion with few reported cases in the literature to guide surveillance and follow-up.

2. Methods

The review was registered with Research Registry (UIN: reviewregistry1127) [2]. A literature search of PubMed, EMBASE, Cochrane Central Register of Controlled Trials and Google Scholar search engine was conducted in March 2021 for reported cases of HSVN.

Search term key words included "hepatic small vessel neoplasm", "hepatic small vessel neoplasms", "hepatic small vessel neoplasia" or "hepatic small vessel neoplasias" under the MESH headings ("Liver Neoplasms/pathology"[Mesh] OR "Liver Neoplasms/surgery"[Mesh]). All reported cases were considered, with no language or publication date restrictions.

Two authors (IG and PM) independently searched and reviewed each article and their bibliography using standardised data collection, in

* Corresponding author. Department of General Surgery, Mater Hospital, Brisbane, Queensland, Australia.
E-mail address: ian.goh@uqconnect.edu.au (I.Y. Goh).

https://doi.org/10.1016/j.amsu.2021.103004
Received 24 September 2021; Received in revised form 30 October 2021; Accepted 31 October 2021
Available online 1 November 2021

accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8] (Fig. 1.) and AMSTAR 2 (Assessing the methodological quality of systematic reviews) [9] Guidelines. All reports with histologically confirmed HSVN were considered. Reports not meeting the diagnostic criteria (presence of infiltrative/invasive border, CD34 positivity, low Ki-67 index, and absence of strong/positive c-myc and p53 on immunohistochemistry) for HSVN as described by Gill et al. [7] were excluded by consensus between IG and PM, and any disagreements were resolved by a third reviewer (CL) or consensus-based discussion. Patient demographics, clinical information, radiological appearance, pathologic findings, clinical management, and follow-up outcomes were recorded.

3. Results

In total 69 publications were identified, of which ultimately 63 were excluded as they were duplicates or not reports of HSVN. Full text papers were assessed for eligibility prior to inclusion.

In addition to the 17 cases described by Gill et al., a further six more cases have been reported in five other articles, thus bringing the total number to 23 [1,7,10–13] (See Table 1.).

3.1. Demographics

All 23 patients were adults, with the median age of 58 (range 24–83 years). There was a male preponderance (17 males and 6 females).

3.2. Risk factors

There was no mention of a syndromic association in any of the cases. This was especially with regards to Sturge-Weber syndrome, given that two of the three HSVN Gill et al. [7] had an activating *GNAQ* mutation.

The most common association amongst the 23 patients was background liver disease. Four patients had underlying cirrhosis, three patients had hepatitis C (of which two had cirrhosis), two had non-alcoholic fatty liver disease, two had steatohepatitis (of which one had cirrhosis), and one had haemochromatosis. Focal nodular hyperplasia was suspected in one patient, and another patient had Crohn's disease with known haemangiomas.

3.3. Tumour frequency, size, location and symptoms

HSVN largely appeared as a single tumour though Gill et al. reported three cases presenting as multiple lesions. Of the 21 cases with size data, the mean tumour size was 2.8 cm, the largest being 15.9 cm [13] (median 2.2 cm, range 0.2–15.9 cm). Regarding symptoms, 22 out of 23 patients were asymptomatic, with the exception being the largest tumour. This was reported as "epigastric fullness" [13]. HSVN occurred in both lobes of the liver.

3.4. Immunohistochemistry

All 23 cases demonstrated positive staining for the vascular marker

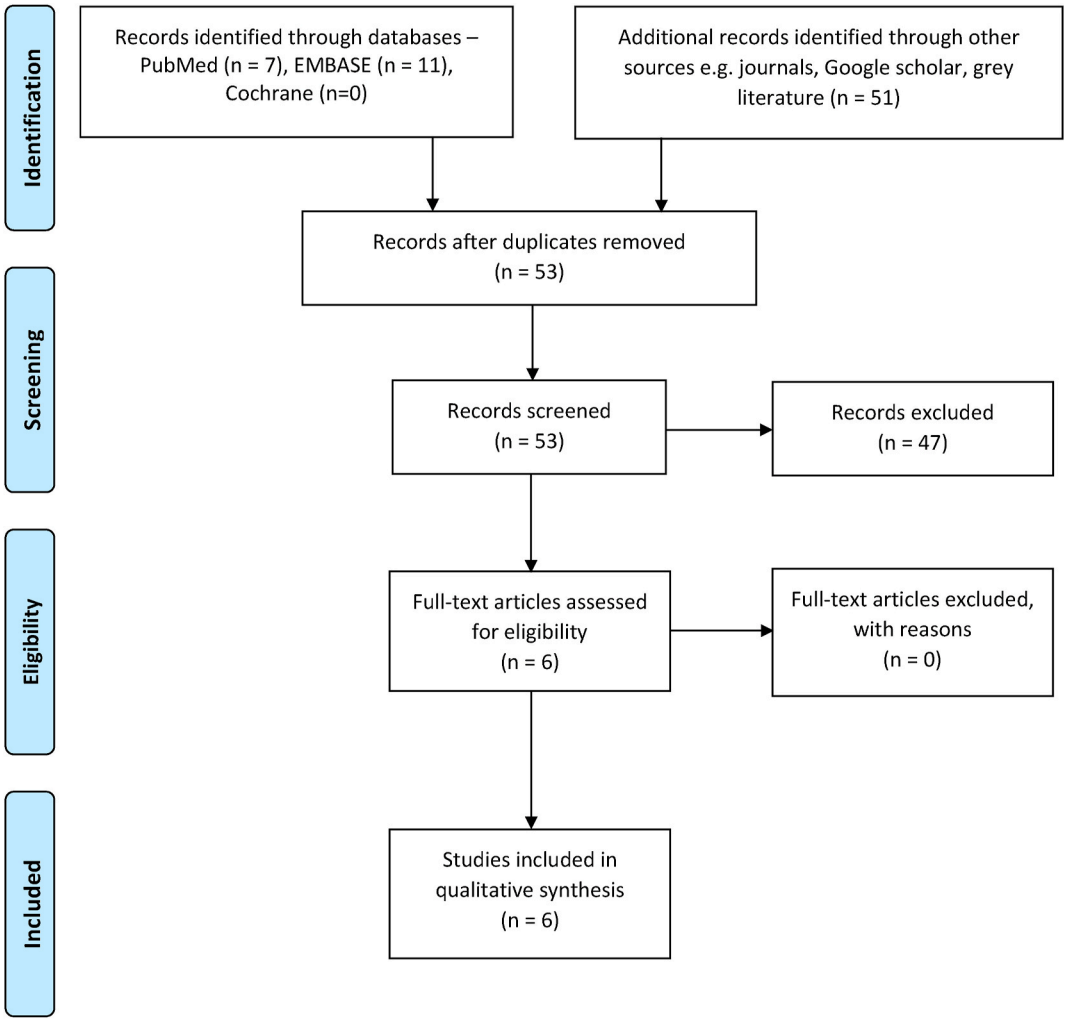

Fig. 1. Literature search according to the PRISMA Guidelines.

Table 1
Patient characteristics of included studies.

Case	Age (y)	Gender	Size (cm)	Clinical background/ Symptoms	Intervention	ARD	Follow-up (months)	Location (Segment or lobe)	CD34	Ki-67 (%)	c-myc[g]	p53[g]
1[a]	83	Male	1.5	Incidental tumour	None	Yes	5	No data	Positive	16/16	14/14	14/14
2[a]	58	Male	0.7	HCV with incidental tumour	Yes – resection	No	12	No data		low (0–8%)	weak	weak
3[a]	57	Male	2	Incidental tumour	No data	No data	No data	No data	Positive			
4[a]	47	Male	1.1	RCC with incidental tumour	Yes – resection	No data	No data	No data				
5[a]	53	Male	2.8	Multiple liver tumours	None	Yes	1	No data	Positive			
6[a]	58	Female	1.5	Incidental tumour at autopsy	None	Not applicable	Not applicable	No data				
7[a]	37	Female	5.5	Incidental tumour at pregnancy	Yes – resection	no	6	No data	Positive			
8[a]	61	Male	1.3	HCV, cirrhosis, ?HCC	None	Yes	1	No data				
9[a]	43	Male	2.2	NAFLD, 50% lesion growth in 4 years	Yes – resection	No	24	No data	Positive			
10[a]	66	Male	1.8	HCV, cirrhosis, ?HCC	Yes – hepatectomy	No data	No data	No data				
11[a]	65	Male	2.2	Bronchial carcinoid, ? metastatic tumour	Yes – wedge biopsy + RFA	Yes	1	No data	Positive			
12[a]	54	Male	4.2	Incidental tumour	Yes – TACE followed by resection	No	13	No data				
13[a]	59	Female	2.5	CHF and renal failure with incidental tumour	Resection	No	1	No data	Positive			
14[a]	24	Female	1	NAFLD with resection of 5.3 cm hepatocellular adenoma	No data	No data	No data	No data	Positive			
15[a]	67	Male	2.7	Elevated LFT and ? FNH	None	Yes	3	No data	Positive			
16[a]	77	Male	3	Incidental tumour	None	Yes	1	No data				
17[a]	65	Male	0.2	Cirrhosis, incidental tumour	Yes – hepatectomy	No	12	No data	Positive			
18[b]	37	Male	2.6	Fatigue, pruritus, Crohn's disease, haemangiomas	Yes – resection	Negative	6 months; no recurrence	II/IV	Positive	<10	Weak	Weak
19[c]	48	Female	Not assessed	Haemochromatosis	No data	No data	No data	Left lobe	Positive	Low	No data	No data
20[c]	67	Female	Not assessed	Hepatic steatosis	No data	No data	No data	VI	Positive	Low	No data	No data
21[d]	62	Male	15.9	IDA, HTN, dyslipidaemia, epigastric fullness, ? HCC	Yes – resection	No	6 months; no recurrence	Left lobe and anterior right lobe	Positive	4.2	Negative	Weak
22[e]	59	Female	2.2	Cirrhosis, obesity	None	No data	No data	VIII	Positive	1	No data	Negative
23[f]	57	Male	2.7	Obesity, HTN	Yes – resection	Yes	14	VII	Positive	5	Negative	Weak

Abbreviations: ARD (alive with residual disease); HCV (hepatitis C virus); RCC (renal cell carcinoma); HCC (hepatocellular carcinoma); FNH (focal nodular hyperplasia); CHF (congestive heart failure); IDA (iron deficient anaemia); HTN (hypertension); TACE (transcatheter arterial chemoembolisation); NAFLD (non-alcoholic fatty liver disease); LFT (liver function test).

[a] Gill et al. [7].
[b] Koschny [10].
[c] Rangaswamy [12].
[d] Walcott-Sapp [13].
[e] Lewis [11].
[f] Mulholland [1].
[g] The pathologic interpretation of c-myc and p53 is reported in several ways in the literature, where a normal pattern of staining can be recorded as either "weak" or "negative"; this distinction is not important as long as it is not strongly positive, which can be seen in angiosarcoma.

CD34. The Ki-67 proliferative index was low (<10%) in all 21 assessed cases. C-myc was weak or negative in all 17 assessed cases, and p53 was weak or negative in all 18 assessed cases.

3.5. Follow-up

Reported follow-up amongst the patients was variable, the shortest being one month and the longest being 24 months, with a mean of seven months. Six patients had positive margins or residual disease, of which the longest follow-up was 14 months with no reported evidence of disease recurrence [1]. The remaining 18 patients had no residual disease. The single longest follow-up was 24 months post resection, with no evidence of disease recurrence.

4. Discussion

4.1. Summary

Benign vascular tumours are the most common hepatic mesenchymal neoplasms. HSVN is a recently recognised vascular tumour, showing features of both haemangioma and AS [7]. Despite limited follow-up data, HSVN appears to demonstrate a benign clinical course with no

reported recurrences or metastatic disease.

Gill et al. presented the most comprehensive case series of HSVN, comprising 17 cases [7]. In this series, HSVN was commonly an incidental finding in adult patients (mean 54 years; range 24–83). Average tumour size was 2.1 cm (median 2.0 cm, range 0.2–5.5 cm). On histologic assessment the tumours were poorly circumscribed and featured infiltration of hepatic parenchyma by anastomosing capillaries, which were lined by bland endothelial cells. Immunohistochemical analysis showed uniform strong positivity for vascular markers (CD34, CD31 and FLI-1). Proliferative fraction, as measured by Ki-67, was low (mean 3.7%). Molecular analysis was performed on three cases. Two tumours demonstrated an activating hotspot *GNAQ* mutation, with one of these tumours also showing an activating mutation in *PIK3CA*.

A recent study has shown HSVN shares similar molecular biology to congenital haemangioma and anastomosing haemangioma with *GNAQ*, *GNA11* and *GNA14* mutations [14]. More reassuringly, these mutations are not found in angiosarcomas [15,16].

Since the initial description by Gill et al., six additional cases of HSVN have been reported [1,7,10–13], giving a total of 23 cases. It is possible lesions recently described as "anastomosing haemangioma" of the liver also represent HSVN [17–19], however on discussion this was excluded as its description was not completely typical of HSVN given the infiltrative nature of HSVN as described by Gill et al. [7].

HSVN arises in adults and shows a male predominance. They can range in size and may potentially give rise to mechanical symptoms due to large size. Four cases presented as multiple lesions [1,7] and it is uncertain if these were synchronous lesions or metastatic disease.

At the present, the imaging characteristics of HSVN are nonspecific, and more data are needed to devise diagnostic criteria for HSVN. Cases with published radiology data [10–13] show strong enhancement on arterial phase and mostly strong enhancement on portal venous phase, with equivocal findings on delayed phases and diffusion-weighted imaging.

In terms of prognosis, it is noted that HSVN has a low recurrence rate regardless of margin status. In the original description by Gill et al. [7] follow-up data were available in 12 patients (range 1–24 months). There was no evidence of disease progression in any of the patients, despite incomplete excision in some cases.

4.2. Limitations

As HSVN is a newly recognised tumour, there are currently few reported cases. It is possible that additional cases meeting the diagnostic criteria for HSVN were previously reported under a different designation, and therefore have not been captured in this systematic review. Longer follow-up of patients, along with radiological criteria for HSVN, might also give a clearer understanding of the biology of HSVN.

5. Conclusion

HSVN is a vascular neoplasm of the liver which can appear histologically similar to hepatic AS. However, unlike AS, all reported lesions have demonstrated benign clinical behaviour with no progression, even with incomplete resection. Despite HSVN being likely benign, the current recommendation is for complete resection and close observation. Long-term follow-up data, will further supplement our understanding of these tumours, guiding future management.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Please state any sources of funding for your research

None.

Please state whether ethical approval was given, by whom and the relevant Judgement's reference number

Not required.

Research registration Unique Identifying number (UIN)

1. Name of the registry:
Research Registry.
2. Unique Identifying number or registration ID:
Reviewregistry1127.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):
https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/606555e625d781001bdf518a/

Author contribution

Ian Y Goh - study concept or design, data collection, data analysis or interpretation, writing the paper.

Patricia Mulholland - study concept or design, data collection, data analysis or interpretation, writing the paper.

Anna Sokolova - study design, data analysis or interpretation, and final approval.

Cheng Liu - study concept or design, data analysis or interpretation, edition and final approval.

Mehan Siriwardhane - study concept or design, data analysis or interpretation, edition and final approval.

Guarantor

Ian Y Goh, Email: ian.goh@uqconnect.edu.au

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.103004.

References

[1] P. Mulholland, I.Y. Goh, A. Sokolova, C. Liu, M. Siriwardhane, Hepatic small vessel neoplasm case report: a surveillance conundrum, Int. J. Surg. Case Rep. (2021) 105742.
[2] Research Registry, Registry of systematic review/meta-analysis [Available from: https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/.
[3] P. Bioulac-Sage, H. Laumonier, C. Laurent, J.F. Blanc, C. Balabaud, Benign and malignant vascular tumors of the liver in adults, Semin. Liver Dis. 28 (3) (2008) 302–314.
[4] D. Maluf, A. Cotterell, B. Clark, T. Stravitz, H.M. Kauffman, R.A. Fisher, Hepatic angiosarcoma and liver transplantation: case report and literature review, Transplant. Proc. 37 (5) (2005) 2195–2199.
[5] G.Y. Locker, J.H. Doroshow, L.A. Zwelling, B.A. Chabner, The clinical features of hepatic angiosarcoma: a report of four cases and A review of the English literature, Medicine 58 (1) (1979) 48–64.
[6] R.T. Groeschl, J.T. Miura, K. Oshima, T.C. Gamblin, K.K. Turaga, Does histology predict outcome for malignant vascular tumors of the liver? J. Surg. Oncol. 109 (5) (2014) 483–486.
[7] R.M. Gill, B. Buelow, C. Mather, N.M. Joseph, V. Alves, E.M. Brunt, et al., Hepatic small vessel neoplasm, a rare infiltrative vascular neoplasm of uncertain malignant potential, Hum. Pathol. 54 (2016) 143–151.

[8] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Int. J. Surg. 88 (2021) 105906.
[9] B.J. Shea, B.C. Reeves, G. Wells, M. Thuku, C. Hamel, J. Moran, et al., Amstar 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both, BMJ 358 (2017) j4008.
[10] R. Koschny, M. Allgäuer, J. Pfeiffenberger, J. Seessle, J. Fuchs, T. Longerich, et al., Case report: a rare cause of a hypervascular nodule in a noncirrhotic liver, Z. Gastroenterol. 57 (1) (2019) 57–60.
[11] S. Lewis, B. Aljarallah, A. Trivedi, S.N. Thung, Magnetic resonance imaging of a small vessel hepatic hemangioma in a cirrhotic patient with histopathologic correlation, Clin. Imag. 39 (4) (2015) 702–706.
[12] B. Rangaswamy, M. Minervini, M. Tublin, B. Sholosh, A.K. Dasyam, Imaging and pathologic findings of hepatic small vessel hemangioma, Curr. Probl. Diagn. Radiol. 48 (6) (2019) 626–628.
[13] S. Walcott-Sapp, E. Tang, S. Kakar, J. Shen, P. Hansen, Resection of the largest reported hepatic small vessel neoplasm, Hum. Pathol. 78 (2018) 159–162.
[14] M.N. Joseph, M.E. Brunt, C.C. Marginean, N.I. Nalbantoglu, M.D. Snover, E. S. Thung, et al., Frequent GNAQ and GNA14 mutations in hepatic small vessel neoplasm, Am. J. Surg. Pathol. 42 (9) (2018) 1201–1207.
[15] R. Murali, R. Chandramohan, I. Möller, S.L. Scholz, M. Berger, K. Huberman, et al., Targeted massively parallel sequencing of angiosarcomas reveals frequent activation of the mitogen activated protein kinase pathway, Oncotarget 6 (34) (2015) 36041–36052.
[16] B. Sam, S.T. Patrick, S. Helen, M. Inigo, L. Peter Van, G. Gunes, et al., Recurrent PTPRB and PLCG1 mutations in angiosarcoma, Nat. Genet. 46 (4) (2014) 376.
[17] B. Merritt, S. Behr, S.E. Umetsu, J. Roberts, K.P. Kolli, Anastomosing hemangioma of liver, J. Radiol. Case Rep. 13 (6) (2019) 32.
[18] J. Lin, J. Bigge, T.M. Ulbright, E. Montgomery, Anastomosing hemangioma of the liver and gastrointestinal tract: an unusual variant histologically mimicking angiosarcoma, Am. J. Surg. Pathol. 37 (11) (2013) 1761–1765.
[19] X. Peng, J. Li, Z. Liang, Anastomosing haemangioma of liver: a case report, Mol Clin Oncol 7 (3) (2017) 507–509.