Primary Hepatic Angiosarcoma: A Brief Review of the Literature

EDITOR'S PICK

I have chosen this paper by Chen et al. as my Editor's Pick because primary hepatic angiosarcoma is a rare, malignant, mesenchymal tumour of the liver, and the diagnostic challenges and its rapidly progressive nature contribute to the poor prognosis seen in clinical practice. There is little published literature on primary hepatic angiosarcoma and therefore this paper reviewing the challenges posed by the tumour will be a helpful guide for clinicians across the globe.

Prof Markus Peck-Radosavljevic

Klinikum Klagenfurt am Wörthersee, Austria

Authors: *Nelson Chen,[1] Aidan (Jia Sheng) Yu,[2] Jihye Jung[1]

1. Princess Alexandra Hospital, Brisbane, Australia
2. Royal Brisbane and Women's Hospital, Brisbane, Australia

*Correspondence to dr.nelsonchen@gmail.com

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Abstract

Primary hepatic angiosarcoma (HAS) is a liver tumour of endothelial cell origin. It is the most common malignant mesenchymal tumour of the liver, but is nonetheless rare, accounting for approximately 0.1–2.0% of all primary liver malignancies. Historically, 25% of HAS cases were associated with occupational or medicinal exposure, but most cases are now considered idiopathic. Patients present with vague signs and symptoms of liver disease, often resulting in late diagnoses; patients may present with acute liver failure or spontaneous rupture of the tumour, but this is rare. Preoperative diagnosis of HAS is difficult because laboratory and radiological findings are often non-specific or unable to discern malignant masses from benign growths. Obtaining a biopsy for histopathological diagnosis of HAS is also difficult because of its vascular and haemorrhagic nature, and reports of death from closed biopsies have been noted. Prognosis is poor because of the disease's diagnostic challenges and the tumour's rapidly progressive and early metastatic nature. The reported median survival is approximately 6 months, with only 3% of patients living >2 years. This paper will review and summarise new and existing publications in the English language literature to provide a better understanding of the challenges posed by HAS.

INTRODUCTION

Primary hepatic angiosarcoma (HAS) is a rare liver tumour of endothelial cell origin. Diagnostic challenges and its rapidly progressive nature contribute to the poor prognosis of the tumour. Historically, 25% of cases were associated with occupational exposures or medicinal carcinogens,[1] but today the majority of cases have no known aetiology. Patients present with vague symptoms and signs of liver disease, and many cases are diagnosed incidentally or at autopsy.[2] Liver resection is the most effective treatment for HAS, but appropriate management requires early work-up and diagnosis.[3] This paper will review and summarise new and existing literature to provide a better understanding of the challenges posed by HAS.

EPIDEMIOLOGY AND AETIOLOGY

Angiosarcomas are rare tumours of endothelial cell origin. Most cases occur in the head and neck, with 6% arising in the liver, making it the fifth most common site for angiosarcomas.[4] HAS is rare and accounts for approximately 0.1–2.0% of all primary liver malignancies, but it remains the most common malignant mesenchymal tumour of the liver.[2,5] HAS predominantly occurs in males in the 6th and 7th decades of life, and most studies have shown a male-to-female ratio of 3–4:1; however, a lower ratio of 2:1 in Asian countries has been reported.[6]

Historically, up to 25% of HAS cases were linked to a known aetiology.[1] Previously, Thorotrast was used as a radioactive contrast and was responsible for a large number of HAS cases during its widespread use between 1928 and 1955.[7] It was mostly deposited in the liver's reticuloendothelial system and has a long biological half-life of 200–400 years.[8] Since the cessation of Thorotrast use in the 1950s, the number of Thorotrast-induced cases has decreased. The latest case report described 65 years of latency, far beyond the average latency period of Thorotrast, which is approximately 20 years.[7] Vinyl chloride monomer, which is involved in the manufacture of plastic, is another well-studied aetiology of HAS and was first described by Creech and Johnson in 1974.[9] It was shown to increase the risk of HAS 10–15-fold, with a latency period of 9–35 years.[10,11] Cases of vinyl chloride monomer-induced HAS are now less common, with worldwide regulations on its emission having been established.[12] In addition, arsenic is also known to cause HAS and is found in contaminated drinking water and pesticides, or used in Fowler's solution to treat asthma, psoriasis, and other conditions.[13] Other proposed associations with HAS include androgenic anabolic steroids, cyclophosphamide, phenelzine, and copper,[12] but these cases are rare and lack a definitive causal relationship.

Some conditions thought to be associated with HAS include von Recklinghausen disease and haemochromatosis.[12] There have been two cases of HAS that have occurred in young patients with dyskeratosis congenita, a bone marrow disease associated with an increased risk of various malignancies.[14] In addition, some studies have considered the relationship of HAS with chronic viral hepatitis; however, results from a study in Taiwan, a hepatitis-endemic country, suggested that there is no increased risk of HAS in patients with a background of hepatitis B or C.[6] The phosphatase and tensin homolog (*PTEN*) tumour suppressor gene and the alternative lengthening of telomeres (ALT) mechanism have also been found to have some association with HAS, but no extensive research is available in this area.[15,16]

PRESENTATION

While 9% of individuals present with manifestations secondary to metastasis,[2] most patients present with non-specific symptoms of liver disease, often resulting in late diagnoses. Abdominal pain, fatigue, weight loss, and anorexia are common symptoms of HAS, but many cases can be asymptomatic.[5] Examination findings include hepatomegaly, jaundice, ascites,[17] and, rarely, hepatic bruits may be audible on auscultation due to the vascular nature of the tumour.[18]

Haemoperitoneum secondary to spontaneous tumour rupture occurs in 17–27% of cases,[17] and should be considered an indicator of a malignant tumour because benign tumours rarely undergo spontaneous rupture.[19] There have also been cases of patients presenting with haemothorax

from diaphragmatic tumour invasion,[20] as well as a case of bleeding oesophageal varices in a patient with no previous carcinogenic exposure or liver disease.[21] Acute liver failure or fulminant liver failure with encephalopathy and coagulopathy are rare initial presentations.[22,23] Other rare presentations include high-output cardiac failure[24] and disseminated intravascular coagulopathy (DIC), which occurs in <5% of cases.[17] Few reports have been associated with Kasabach–Merritt syndrome, which is DIC occurring in any vascular tumour.[25]

INVESTIGATIONS

Serology can be normal in some HAS cases,[26] but results usually show non-specific elevations indicative of liver disease, with 97% of patients displaying at least one raised liver enzyme;[17] alkaline phosphatase is the most commonly elevated liver enzyme.[18] Hyperbilirubinaemia may also occur, particularly in progressive disease.[27] Thrombocytopenia occurs in approximately 54% of patients,[17] secondary to local destruction of platelets within the tumour. The sequestration of platelets and local intravascular destruction of clotting factors[28] both contribute to the pathophysiologic process of DIC, which has been well-described in the literature.[28,29] Anaemia is another common finding in patients with HAS, with 8% of patients developing microangiopathic haemolytic anaemia as a result of the use of blood components by the tumour.[17] Anaemia can also be explained by spontaneous tumour rupture. Leucocytosis has also been described, with one particular case reporting extreme leucocytosis secondary to a leukemoid reaction, with a white cell count of 74.7×10^9.[30] Hypercalcaemia can be elevated in cases associated with bone metastases.[17] There are no specific tumour markers associated with HAS; carcinoembryonic antigen,[23] alpha-fetoprotein, and cancer antigen 19-9 may show mild elevations,[11] but none are specific to HAS.

Appearances on conventional ultrasound are non-specific, and masses typically demonstrate different echotextures depending on the presence of necrosis and haemorrhage.[22,31] Colour Dopplers may display minimal blood signals in large masses only.[31] In contrast-enhanced ultrasound, HAS can present with peripheral nodular or rim enhancement without centripetal filling and there can be a reticular or chaotic pattern of arterial enhancement.[32] A non-enhancement area in the centre of the large mass is another commonly reported feature in contrast-enhanced ultrasound.[31]

Similarly, appearances on unenhanced computed tomography (CT) are non-specific, and the hypervascular and heterogenous nature of HAS is better depicted in dynamic CT and magnetic resonance imaging (MRI). Currently, there are no known pathognomonic features for HAS.[33] Tumours generally display heterogenous enhancement on the late arterial phase with progressive enhancement on the portal venous and delayed phases.[34-36] The pattern of progressive centripetal nodular enhancement mimicking cavernous haemangioma has been previously described but is now thought to be atypical for HAS.[35] The nodular foci found in HAS can be distinguished from benign haemangiomas because they tend to be more bizarre in shape, even if centripetal enhancement is observed, and with ring enhancement;[34,35] some cases may demonstrate a centrifugal enhancement or 'reverse haemangioma' pattern.[34] Arterioportal shunting is not commonly seen in haemangioma and its presence favours the diagnosis of HAS,[37] while diffuse HAS can rarely present as pseudo-peliosis with infiltrating micronodules filled with contrast.[35]

This progressive enhancement pattern is even more noticeable in dynamic contrast MRI due to the availability of delayed phase images.[35,38] On delayed phase images, dominant masses exhibit progressive but incomplete enhancement. In addition, nodules can appear uniformly hyperintense due to complete filling and lesions show peripheral rim and central septal-like or linear progressive enhancements in comparison to progressive centripetal nodular enhancement found in haemangioma.[38] In comparison to haemangiomas, the enhancement of angiosarcomas is usually less than that of the aorta.[39]

On unenhanced T1-weighted images using MRI, dominant masses can present with decreased signal with focal areas of high signal intensity, suggesting the presence of haemorrhage.[36] On T2-weighted images, dominant masses display

increased signal intensity and are generally hyperintense relative to the surrounding hepatic parenchyma.[34,38] Nodular cases mostly display moderate-to-high signal intensity with varying intralesional areas of low signal intensity. Elevations of the apparent diffusion coefficient level have also been described when compared to other hepatic malignancies, but the values are lower compared to those seen in benign cysts and haemangiomas.[38] Foci with varying amounts of signal intensity, progressive enhancement, and intratumoural haemorrhages mirror the heterogenous architecture of hepatic angiosarcomas.[39] Lastly, hepatic angiography is another tool used for diagnosis and the contrast medium routinely migrates into small vascular lakes with central areas of hypovascularity and peripheral contrast staining. The most characteristic angiographic feature is the intense peripheral stain late in the arterial phase lasting 30–40 seconds.[40]

DIAGNOSIS

Diagnosis of HAS is challenging due to non-specific presentations and investigation findings, which often overlap with the findings from other vascular tumours. Preoperative diagnosis is important for the planning of management; for example, tumours such as epithelioid haemangioendothelioma may be treated with an orthotopic liver transplant, whereas HAS is a contraindication for transplantation.[41]

Obtaining tissue samples for histopathological diagnosis is difficult in HAS. Haemorrhage due to the vascular nature of the tumour remains the most controversial complication, occurring in approximately 27% of patients and 5% of cases result in death.[17] The incidence of haemorrhage after percutaneous biopsy in HAS is much higher than biopsies for other liver tumours, such as hepatocellular carcinoma.[42] This is substantiated by two notable cases of death secondary to haemorrhage, both from fine needle biopsies.[43,44]

Many reports recommend open rather than closed biopsies because of better visualisation and easier haemostasis.[17,40] The diagnostic yield is also reported to be higher with open biopsies than closed biopsies (65% versus 25%, respectively; $p<0.01$).[17] Reports on fine needle aspiration vary, with some supporting their use[45] while others report inconclusive results with all fine needle aspiration cases (N=4), requiring further biopsies to validate diagnosis.[32] Percutaneous biopsies are reported to be more sensitive because samples contain larger core tissues without fragmentation.[42] They are also safer and faster to perform, without significant complications or mortality.[35,42] Koyama et al.[35] reported that 78% (7 out of 9) of their biopsies yielded diagnostic specimens without complications. Similarly, Kang et al.[42] performed a multicentre study in South Korea and concluded that 96.9% (32 out of 33) of cases were diagnostic on first biopsy, while the remaining 3.1% (1 out of 33) were diagnosed on the second biopsy. They reported bleeding occurrences in 9.1% (3 out of 33) of patients, which were managed by transfusion (2 out of 3) and hepatic artery embolisation (1 out of 3), resulting in no mortality.[42] Transjugular liver biopsies are reportedly safer and have fewer complications than percutaneous biopsies, but have less diagnostic power.[40]

Regardless of the approach used, false-negative biopsies remain an issue due to a high frequency of necrotic and haemorrhagic foci within the tumour.[17,32,46] Occasionally, non-malignant changes, such as portal tract and sinusoidal fibrosis, are identified without malignant foci;[17,46] as a consequence, as many as one-third of patients are diagnosed during autopsy,[17] while others are diagnosed after liver transplant.[11,46]

PATHOLOGY

Macroscopically, HAS is characterised by four growth patterns: multiple nodules, large dominant mass, mixed pattern of dominant mass with nodules, and, rarely, a diffusely infiltrating micronodular tumour.[35,38] Lesions can vary in colour, ranging from pale white-yellow-grey[5,22,31] to red-brown,[26] and the margins are usually poorly defined,[2] but well-demarcated borders have also been reported.[5] The tumours are described as spongy[24] and are usually heterogenous in appearance, with alternating areas of haemorrhagic foci, large intraparenchymal cystic spaces filled with thrombotic content,[29] and gross necrotic areas.[5,26,31]

Microscopically, HAS is composed of malignant atypical endothelial cells[47] that are pleomorphic and may be round, irregular, or spindle-shaped.[8,18] Tumour cells contain prominent chromatin[33] and atypical hyperchromic and elongated nuclei with frequent mitoses.[18] Erythrophagocytosis has also been described.[8,45] Neoplastic cells proliferate in single or multiple layers[37,47] and infiltrate along preformed vascular channels, such as dilated sinusoids,[18] as well as central veins and portal vein branches.[24,29] Tumour cells may also form their own disorganised[34] anastomotic vascular channels,[2,28,46,47] shape solid nodules or nests,[2,38] or form cavernous spaces due to the loss of adjacent hepatocytes,[18] which may mimic cavernous haemangiomas.[35] More than one vascular pattern may be found in a single patient[46] and the predominating pattern differs in each case.[35] Surrounding hepatocytes may be hyperplastic[18] or atrophic.[27] Separation of atrophic hepatocytes and sinusoidal dilatation is sometimes mistaken as a sign of peliosis hepatitis.[11] Areas of haemorrhage, necrosis, infarction, and calcifications are also frequently described;[18,31,33] for example, one case series reported that 83% (10 of 12) of specimens contained necrosis, while 82% (9 of 11) contained haemorrhage.[35]

While atrophic hepatocytes are thought to be indicative of progressive HAS,[48] hyperplastic hepatocytes and cells lining irregularly dilated and atypical sinusoids are believed to be early changes.[8,48] Precancerous changes have been described by several authors in the 1970s and 1980s when the relationship concerning HAS and occupational exposure was brought to light. Popper et al.[49] reviewed 117 cases and believed sinusoidal dilatation and fibrosis were the predominant early changes. They also concluded that the pattern and evolution of HAS were the same irrespective of aetiology, which was confirmed in another review several years later.[14] el Zayadi et al.[50] performed a retrospective review of cases associated with agricultural pesticides and reported no histopathological differences between idiopathic cases and those patients exposed to pesticides.

There are no specific markers suggestive of HAS and, while some are more sensitive than others, they should only be used alongside other investigations to assist diagnosis. It may also be possible for the expression of markers to be variable within the tumour.[18] Wang et al.[47] tested a cohort of HAS samples and concluded that *ERG* expression was the most sensitive and specific marker, with a 100% sensitivity (n=24), followed by CD34 (87.5%), CD31 (87.2%), and FVIII-rA (41.7%). Other immunohistochemical, tumour, and protein markers that have been reported include CD10,[22] CD117,[51] cytokeratin,[47] FLI-1,6 D2-40,[6] and Ki-67.[22]

TREATMENT

The most promising HAS treatment to date is surgical resection of the tumour;[2,3,12] currently, radical surgery with R0 resection is the only curative treatment.[51] Combining adjuvant chemotherapy with surgery gives the highest chance of cure, with a reported median survival of approximately 17 months.[3] In comparison, liver transplant is contraindicated due to high recurrence rates and poor survival post-transplant; the median survival after transplant is <7 months and no patient has survived >23 months.[41] The intrinsic radioresistant property of HAS means that radiotherapy has largely been abandoned as a treatment option.[52]

Many chemotherapy regimens have been described in the literature but no routine has proven to be notably superior to the others. Kim et al.[52] demonstrated improved survival in 50% (n=2) of patients with 5-fluorouracil/carboplatin/doxorubicin/ifosfamide and reported that paclitaxel may be used as a salvage chemotherapy based on its antiangiogenic properties.[52] Others have demonstrated partial response with the mesna/doxorubicin/ifosfamide/dacarbazine regimen.[53] Newer molecular therapies, including bevacizumab, sorafenib, and sunitinib, have demonstrated limited efficacy and cannot be recommended without further studies.[51,52] Single-agent chemotherapy regimens, including dacarbazine, cyclophosphamide, and doxorubicin, have also been used with disappointing results.[25]

More recently, the potential role of the Hippo signalling pathway, which regulates cell proliferation and apoptosis, has been explored in the biological treatment of angiosarcomas.[54] *YAP* is an oncogene involved in this pathway and CD31 regulates endothelial cell function and redox status via *YAP*.[55] Angiosarcoma cells

have been subclassified based on phenotypical expression and it was found that CD31^{low} was more common in angiosarcomas than CD31^{high} and was associated with increased YAP, making the tumour more chemoresistant to agents such as doxorubicin.[54] Venkataramani et al.[54] demonstrated *in vitro* that pazopanib, an effective YAP inhibitor in cancer cells, was effective when used with doxorubicin in resensitisation of CD31^{low} to chemotherapy.[54] Also of note, one retrospective paper found that 30% of a primary angiosarcoma cohort used ALT as the telomere maintenance mechanism and this was highly associated with HAS, with two-thirds of the population positive for ALT. They also reported that ALT-positive cells were sensitive to ATR kinase inhibitors. However, further *in vivo* trials of ATR kinase inhibitors and pazopanib with doxorubicin are required to delineate the benefits and efficacies for the treatment of HAS.[16]

Transarterial embolisation is the modality of choice when patients present with an intrahepatic bleed to achieve haemodynamic stability.[56] Transcatheter arterial chemoembolisation may also be effective in the treatment of patients with dominant lesions with or without metastases. Park et al.[56] suggested that a combination of lipiodol and cisplatin may benefit patients with large dominant masses and few or no intrahepatic metastases, after noting a reduction in tumour size in 50% of patients in their study (n=2). Ozden et al.[57] also described the use of prophylactic chemoembolisation with lipiodol, adriamycin, and mitomycin; the study patient had been alive and recurrence-free for 5 years and 4 months at the time of study publication in 2003.

PROGNOSIS

The median survival after diagnosis of HAS is approximately 6 months, with 3% of patients living >2 years.[3,12,17] In patients who undergo local excision with or without adjuvant chemotherapy, the median survival is around 17 months.[3] In resectable cases, positive resection margins correlate more with poor prognosis as opposed to the size of the tumour; other prognostic factors include poorly differentiated tumours, multinodular and diffuse tumours, and haemoperitoneum with tumour rupture.[6,12,52,57] Hepatic failure is the cause of death in approximately 50% of patients and haemoperitoneum in 25% of patients, followed by metastatic disease, infection, and, rarely, renal failure and congestive heart failure (3% of deaths).[3,17,18,25,29] The lung is the most common metastatic site, followed by the spleen and bone.[17,35,52] Other sites reported include brain,[6] adrenal glands,[58] pericardium and myocardium,[58] kidneys,[58] stomach,[22] left gastric vein,[22] small bowel,[58] and ascending colon.[58,59] Distant metastases are evident in >60% of cases post-mortem[17] and spontaneous tumour rupture carries a poor prognosis, even if bleeding is treated with emergent transarterial embolisation or surgery.[27,56] This complication has been reported in approximately 17–27% of patients.[17] The longest survival to date is a 47-year-old woman who was recurrence-free at 10 years post operation.[12]

CONCLUSION

Early diagnosis and management of primary HAS is critical in patients with a potential lesion; however, this is difficult as most patients present with vague signs and symptoms, non-specific investigations indicative of liver disease, and tumour markers that are often unremarkable or misleading if positive. HAS cases have been accurately diagnosed on both dynamic CT and MRI, where the heterogeneous and vascular nature of the tumour are best depicted. However, there are still no pathognomonic imaging features and, in certain cases, the imaging findings of HAS still overlap with those of benign vascular tumours. Ultimately, a histopathological diagnosis is the only way to confirm HAS. While many early papers advised against percutaneous liver biopsies in light of several fatal cases, more recent studies have demonstrated better outcomes with less complications. Regardless, false-negative biopsies will continue to occur given the pathological process of HAS and surgical resection is the only curative treatment available, particularly in patients with large dominant masses. Several reports on biological and chemotherapy agents are available but more research is required to identify which regimen is most effective. Until then, the poor prognosis remains an issue for HAS patients because of the tumour's rapidly progressive nature and tendency to metastasise early.

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