

# Angiosarcoma of the Liver: Imaging of a rare salient entity

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Radiology Case. 2014 Aug; 8(8):24-32 :: DOI: 10.3941/jrcr.v8i8.1693

## ABSTRACT

Hepatic angiosarcomas are rare mesenchymal tumors with few case series and reports describing their imaging findings in the last two decades. The computed tomography and magnetic resonance imaging findings are variable and may appear like hemangioma at one end of the spectrum and hepatoma at the other end. The use of hepatocyte specific contrast on magnetic resonance imaging may also be insufficient in making a reliable imaging diagnosis. These tumors can easily mimic hypervascular liver cancer, atypical hemangioma or metastases. This case report highlights the imaging features of this entity and also underlines that, this tumor should always be considered as a differential diagnosis for hypervascular tumors in cirrhotic patients. The current imaging paradigms for its diagnosis are also discussed.

## CASE REPORT

### CASE REPORT

A 71-year-old gentleman was admitted to our hospital with a 1 month progressive history of feeling of lump and heaviness in the right hypochondrium. There was no history of jaundice or fever. No other constitutional symptoms were present. On admission, his physical examination showed a firm lump in the right hypochondrium which was inseparable from the liver margins. His laboratory tests showed a normal Alpha fetoprotein (AFP) (3.5 U/ml) (reference range: 10-20 ng/ml). The liver function tests including serum bilirubin and liver enzymes were not elevated. The patient subsequently underwent a dynamic triple phase computed tomography (CT) of the abdomen. It showed two, rounded, ill-defined lesions in the early arterial phase with peripheral hypervascularity in the segment-IV and caudate lobe (Figure 1A). On portal venous phase (PVP), the caudate lobe lesion appeared hypodense compared to rest of the heterogeneously enhancing liver parenchyma; however the segment IV lesion showed progressive centripetal heterogeneous enhancement. There was no evidence of contrast washout (Figure 1B). The liver outlines appeared irregular and lobulated. Magnetic resonance imaging

(MRI) was performed with hepatocyte specific contrast (Gadobenate Dimeglumine, Multihance, Bracco). These lesions were moderately T2 hyperintense (Figure 2A) and demonstrated restricted diffusion on diffusion weighted imaging (Figure 2B). On contrast administration, mild early arterial peripheral vascularity around segment-IV, lesion was seen (Figure 2C) with progressive filling in of the segment-IV and caudate lobe lesions on PVP and equilibrium phase (Figures 2D, E). The liver parenchyma did not reveal any focal hypointense lesions and appeared mildly heterogeneous. It showed diffuse hepatocyte specific contrast enhancement with predominant iso-intense signal on the delayed hepatobiliary phase (Figure 2F). Based on the combined imaging findings of dynamic CT and MRI, a diagnosis of an atypical vascular tumor with differential diagnosis of hemangioma, hepatoma and metastases with underlying diffuse liver parenchymal disease was made. The patient however refused biopsy or any sort of intervention and was managed conservatively. After 4 months the patient returned with worsening symptoms and increase in the lump size. A follow up CT showed a massive increase in the size (more than double) of the lesions with multiple new lesions in both lobes of liver (Figures 3A,B).The

lesions showed gross arterial hypervascularity (Figure 3A). The PVP images revealed multiple ill-defined, predominantly, peripherally enhancing lesions with central areas of hypodensity (Figures 3C, D). The liver parenchyma appeared diffusely heterogeneous (Figure 3D). The repeat AFP levels were also normal. This time however the patient consented to biopsy, which showed sinusoidal and solid growth pattern with atrophic benign hepatocytes at low power magnification (Figure 4A) and atypical endothelial cells displaying irregular hyperchromatic nuclei at high power magnification (Figure 4B). On Immunohistochemistry the malignant endothelial cells showed strong CD34 immunostaining (Figure 4C) consistent with hepatic angiosarcoma.

The patient was offered chemotherapy which he refused and died within 6 months from the date of diagnosis.

## DISCUSSION

### *Etiology & demographics*

Angiosarcoma is a primary mesenchymal tumor of endothelial cell origin with anastomosing vascular channels. Its hepatic subset is found predominantly in males (male: female ratio of 3:1) [1, 2]. It is usually seen to affect the soft tissues of the scalp, head and neck followed by breast as a secondary tumor in patients who receive radiation therapy [3]. Hepatic angiosarcoma is known to have association with carcinogens including vinyl chloride, thorotrast, and arsenic [4]. Liver is an uncommon site for its origin. The malignancy has a small association with Von Recklinghausen syndrome and hemochromatosis [5, 6]. Of all the primary liver cancers barely 2% are reported to be angiosarcoma; however, it still ranks at the third place in the list of most common primary liver malignancies [4,7-8]. It usually affects the elderly (50-79 years) and has a very poor prognosis with median survival rate of 6 months to 2 years [4, 8]. The treatment options are limited and include surgery if the tumor is resectable, followed by chemotherapy or radiotherapy without significant survival benefits [9 - 11]. Early metastases are also a feature of this disease and hence high recurrence with metastasis makes it a difficult tumor to treat even with liver transplant [12].

### *Clinical & imaging findings*

The clinical symptoms of hepatic angiosarcoma are usually non-specific with abdominal fullness, malaise and fatigue. Liver specific changes in laboratory markers such as bilirubin levels, altered protein- albumin/ globulin ratio or raised liver enzymes are seen only in large tumours or in clinically advanced cases. AFP is not elevated in majority of these cases and physical examination shows firm hepatomegaly [7]. Spontaneous rupture of the tumor in the liver and associated peritoneal hemorrhage is a well-known complication seen in approximately in 27% of patients [8, 13]. Imaging is usually the first step in the investigation with dynamic CT or MRI being the modalities of choice to characterize the lesion and monitor the complications. Hepatic angiosarcoma can present as multiple lesions, solitary large mass or as a mixed type of tumor. They usually show early arterial enhancement followed by progressive filling in of contrast within the lesion, contrary to washout seen in

hepatocellular carcinoma [14]. The hypervascular pattern of liver angiosarcoma is usually different from other vascular tumors in the liver, such as hepatoma or hemangioma. The tumor can be solitary or multifocal, however majority of the patients have multiple lesions at the time of presentation with few large tumor masses. Non contrast scans may show areas of heterogeneity with hemorrhage. Post contrast scans show variable and non-conforming pattern of hypervascularity within and around the rim of the lesions. Equilibrium and delayed phases may show centripetal filling in of contrast in the tumor nodules. However most of these nodules still remain hypodense in contrast enhancement compared to rest of the liver parenchyma.

On MRI there is diffusion hyperintensity with variable ADC values which are higher than the mean seen in other hepatic malignancies but low ADC values compared to those seen in benign cysts and hemangiomas [15]. This case highlights the unusual imaging findings of liver angiosarcoma on dynamic enhanced CT as well as MRI with hepatocyte specific contrast with significant progression of the disease in 3 months. The imaging features of angiosarcoma with hepatocyte specific contrast which has an additional window for scanning the patient at a delayed time interval of 90-minutes or more were observed. The tumor appeared isointense and almost homogeneous compared to rest of the liver in the delayed hepatocyte specific phase. These findings steered the diagnosis towards an atypical hemangioma, rather than angiosarcoma. Hence while performing MRI with hepatocyte specific agents; it has to be kept under consideration that lesions which appear homogenous on delayed phase may not always be suggestive of benign lesions.

Angiosarcoma is FDG PET (Fluoro deoxy glucose Positron emission tomography) avid and PET is generally used for detection of distant metastases which are usually present at the time of presentation [9, 28].

### *Treatment & prognosis*

Treatment usually depends on the stage at which the tumor is diagnosed. If the lesion is resectable, then surgery with tumor excision and partial hepatectomy is the treatment of choice [2] However due to the silent course, early distant metastases and asymptomatic nature of the disease, most of these tumors are unresectable at the time of presentation. Radiotherapy is not the therapy of choice since angiosarcoma is not known to be radio-sensitive [9]. Hence, usually, palliative chemotherapy with agents like 5-FU, carboplatin, doxorubicin, ifosfamide, paclitaxel, and bevacizumab is the most commonly used treatment option [9]. Trans-arterial chemotherapeutic embolisation has been used extensively for more aggressive tumors [16].

Selective internal radiation therapy (SIRT) using intrahepatic arterial infusion of <sup>90</sup>Yttrium microspheres has also been used at few centres [17, 18].

Trans-arterial embolisation of the primary tumor is the modality of choice, when there is a risk of spontaneous bleed and tumor rupture which can further lead to tumor seedling into the peritoneum. This also helps in attaining hemodynamic stability [19, 20].

The prognosis of primary hepatic angiosarcoma is poor. As proven in literature, untreated tumors have survival rate of not more than 6 months and median survival rate of 6 months to 2 years even after therapy [1, 4]. Resectable tumors have better prognosis than unresectable tumors. Infiltration of tumor cells into the resected tumor margin has shown poor survival rates. Higher recurrence is also seen in this group [9]. In addition, poor survival was noted in cases of hemoperitoneum due to tumor rupture [16, 14].

#### Differential Diagnoses

The differential diagnoses would include hemangioma, hypervascular metastases and atypical hepatocellular carcinoma (HCC). Hemangioma is a close contender as a differential diagnosis since it exhibits arterial phase enhancement, although, with peripheral partial discontinuous nodular pattern followed by delayed centripetal filling in. A central hypodense area, within the hemangioma is seen with peripheral enhancement in more than 90% population [22]. Angiosarcomas have been confused with cavernous hemangioma since similar progressive enhancement due to multiple vascular channels interspersed with fibrous septae is seen in both tumors [21]. However the key difference remains that the attenuation of hemangioma is always close to the opacification of large vessels, like aorta, which is not usually seen in angiosarcoma [22, 23].

Multiplicity of lesions in angiosarcoma can make its differentiation from metastases (especially hypervascular neuroendocrine lesions) a challenge. The presence of a dominant mass with smaller heterogenous soft tissue lesions may also appear similar to metastatic deposits of varying sizes. The presence of multiple associated splenic deposits is liable to further complicate the picture, however this feature itself, is a clue to the diagnosis of Angiosarcoma, which is seen to frequently metastasize to the spleen [29].

HCC usually shows classical arterial phase hypervascularity with washout in the PVP and equilibrium phases on both CT and MRI. The lesions appear hypoattenuating to rest of the liver in the delayed phases. Multifocal angiosarcoma show early arterial phase hypervascularity, with or without washout in the delayed phase. Some patients, on the contrary show partial progressive delayed enhancement.

Ultrasound shows heterogenous echogenicity in both hepatoma and angiosarcoma. Hemangiomas are usually echogenic in appearance but may sometimes appear isoechoic.

CT and dynamic MRI are the modalities of choice for investigation in today's era. TC-99m-labeled red blood cell scintigraphy is very sensitive for diagnosis of hemangioma and may be useful in differentiating angiosarcoma from large cavernous hemangiomas [25]. Triple tracer scintigraphy may be an effective diagnostic test for HCC in case of suspicion [26].

PET (positron emission tomography) has also been used to diagnose distant spread of disease in hepatoma and angiosarcoma and rarely to diagnose these [27].

An atypical vascular lesion in elderly patients with underlying cirrhotic liver isn't essentially representative of hepatocellular carcinoma. In the background of normal AFP, hypervascular lesions showing variable washout can represent uncommon lesions like angiosarcoma. Also, hypervascular bizarre solitary or multiple lesions showing atypical enhancement pattern not conforming to that of hemangiomas also deserve close monitoring and further investigation. Progressive centripetal contrast filling with variable heterogenous pattern could be a lead pointer to hepatic angiosarcoma [15, 24].

#### TEACHING POINT

Angiosarcoma of the liver is a rare mesenchymal tumor which can present in patients with underlying liver cirrhosis. In the current clinical scenario, it can present without the history of carcinogen exposure with which it is known to be associated. It has variable patterns of enhancement with a few salient distinctive imaging pointers which should be kept under consideration when reporting atypical hypervascular tumours in the liver.

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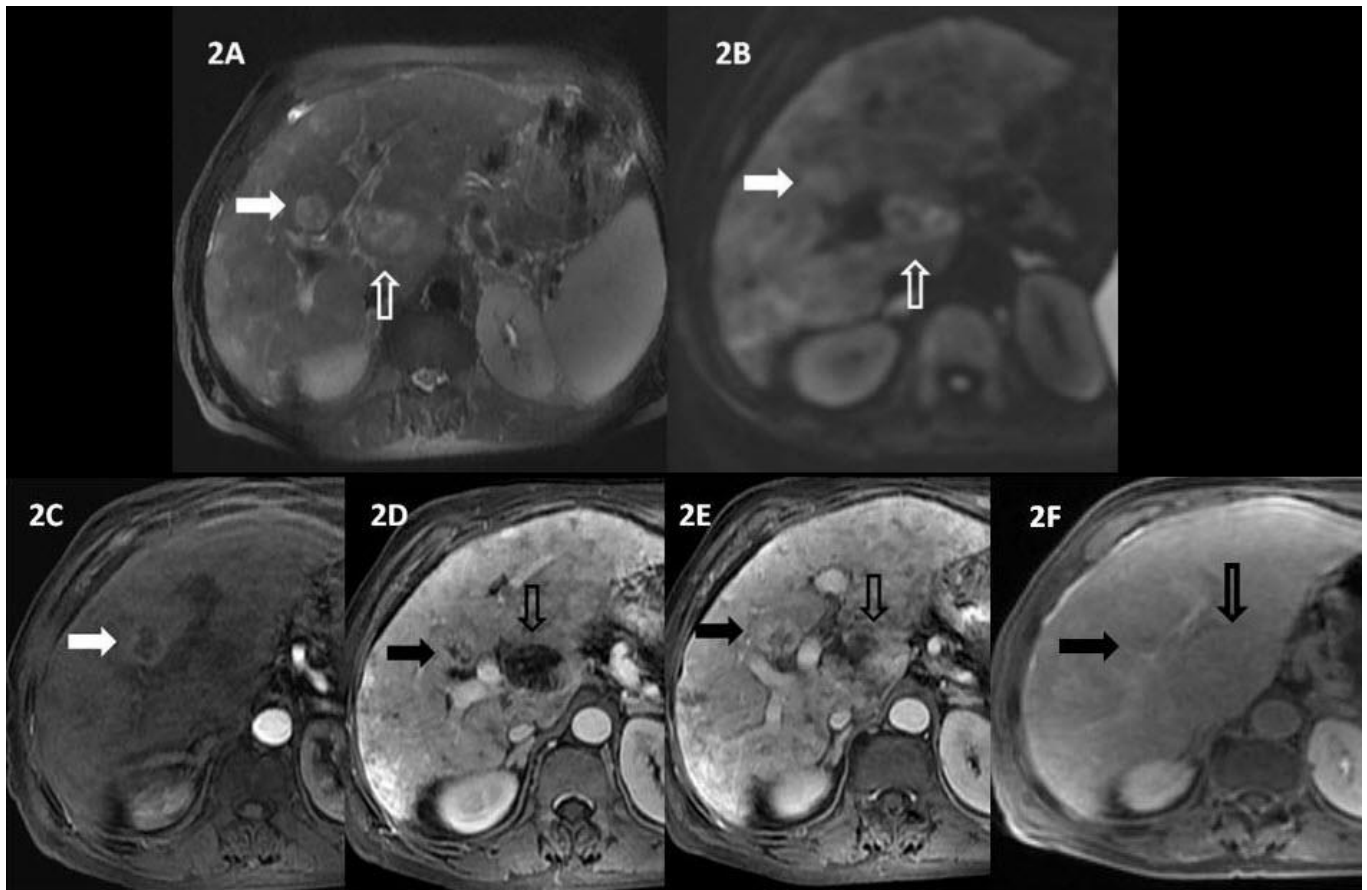
FIGURES



**Figure 1:** 71-year-old man with hepatic angiosarcoma on dynamic triple phase CT

1A. FINDINGS: Arterial phase of the contrast-enhanced CT axial image shows, two iso-hypo attenuating lesions with peripheral arterial enhancement, in the caudate lobe ( white open arrow) and the other in segment IV ( white block arrow) of liver. TECHNIQUE: Scan mode - Helical, Routine time = 0.6 secs. Rotation length - Full, Detector coverage = 40 mm, Helical thickness - 5mm, Pitch and speed (mm/ rot). 984:1/ 39.37 kV, 120, mAs - modulated 120-600 (as per body thickness) contrast - Iomeron400mg/dl.

1B. FINDINGS: Portal-venous phase of contrast-enhanced axial CT image shows progressive centripetal heterogenous contrast enhancement of the segment IV lesion (Black block arrow) and minimal, peripheral as well as faint central enhancement of the caudate lobe lesion (black open arrow). TECHNIQUE: Scan mode - Helical, Routine time = .6 secs. Rotation length - Full, Detector coverage = 40 mm, Helical thickness - 5mm, Pitch and speed (mm/ rot). 984:1/ 39.37, kV, 120, mAs - modulated 120-600 (as per body thickness) contrast - Iomeron400mg/dl.



**Figure 2:** 71-year-old man with hepatic angiosarcoma on hepatocyte specific contrast enhanced dynamic MRI

2A. FINDINGS: Fat-suppressed T2-weighted image, image performed 1 day after the dynamic CT shows rounded hyperintense lesions in segment IV (white block arrow) and in caudate lobe (open white arrow). TECHNIQUE: MRI with T2 weighted fat suppressed sequence (fast spin echo) TR- 3000, TE - 81.5 Band width - 125KH2, FOV - 40 x 40, Matrix - 288 x 192

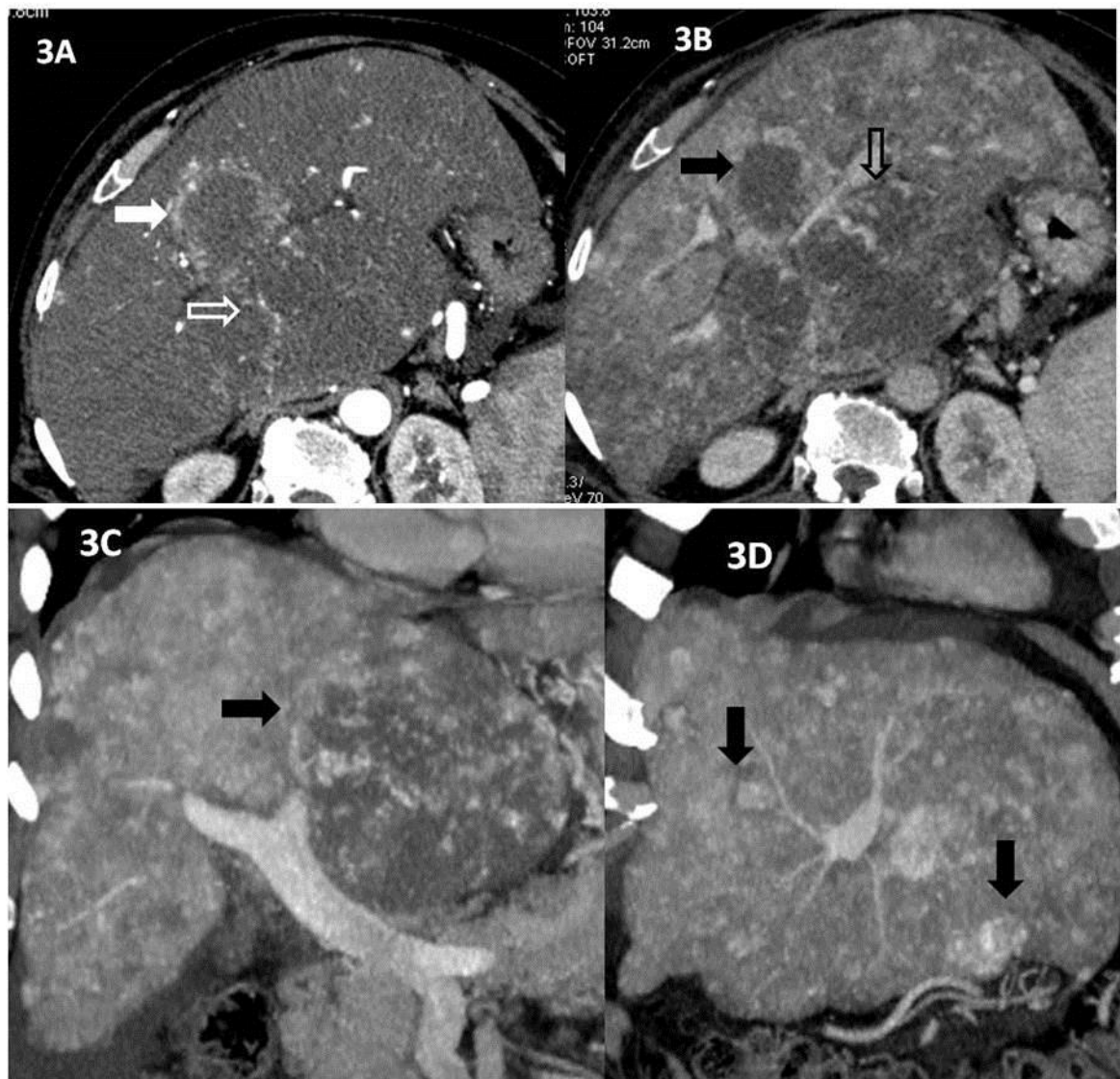
2B. FINDINGS: The axial diffusion weighted image of b value 1000 shows corresponding hyperintensity of the two lesions seen on T2WI (white block and open arrows). TECHNIQUE: TR- 7500 TE- 64.6, Bandwidth - 250 x H2, FOV 44 x 44, Matrix - 96 x 128, NEX - 8 B-value = 1000

2C. FINDINGS: The arterial phase contrast-enhanced gradient echo T1weighted axial MR image shows faint peripheral rim enhancement of the segment IV lesion (white block arrow) only. TECHNIQUE: TR- 3.7, TE - 1.8, Band width - 83.2 KH2, TI - 5, Matrix - 288 x 192, Contrast- Gadobenate Dimeglumine injection, 529 mg/mL

2D FINDINGS: The portal-venous phase contrast-enhanced axial T1 weighted MR image reveals progressive enhancement of the segment IV lesion (block black arrow) and heterogenous peripheral enhancement of the caudate lobe lesion. TECHNIQUE: TR- 3.7, TE - 1.8, Band width - 83.2 KH2, TI - 5, Matrix - 288 x 192

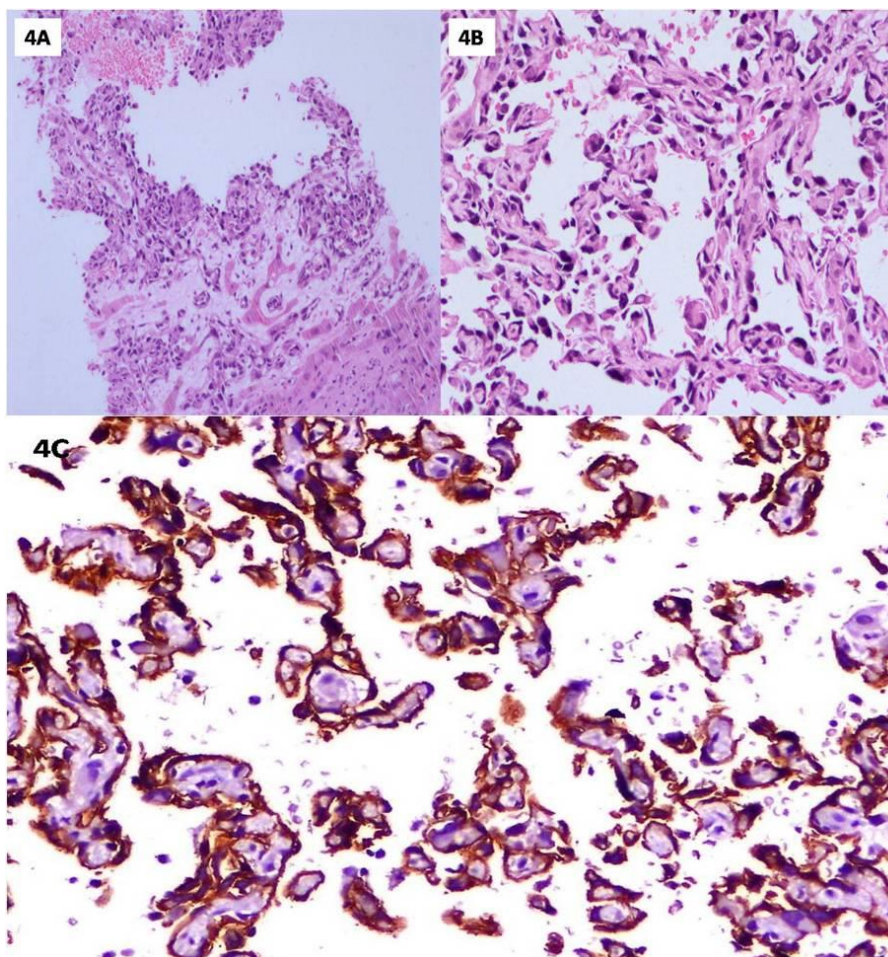
2E. FINDINGS: The equilibrium phase contrast-enhanced axial MR image shows centrifugal heterogenous enhancement of both lesions (black block and open arrows) however density of enhancement is less than that of aorta in all phases. TECHNIQUE: TR- 3.7, TE - 1.8, Band width - 83.2 KH2, TI - 5, Matrix - 288 x 192. Contrast-- Gadobenate Dimeglumine injection, 529 mg/mL

2F. FINDINGS: The delayed hepatocyte phase after 120 minutes shows almost homogenous enhancement of the entire liver parenchyma without any obvious lesion. TECHNIQUE: TR- 3.7, TE - 1.8, Band width - 83.2 KH2, TI - 5, Matrix - 288 x 192. Contrast- Gadobenate Dimeglumine injection, 529 mg/mL



**Figure 3:** Follow up scan after 4 months of 71-year-old man with hepatic angiosarcoma on dynamic triple phase CT.  
3A. FINDINGS: The arterial phase contrast-enhanced CT axial image shows increase in size of the two lesions, in the caudate lobe (white open arrow) and segment IV of right lobe (black block arrow) showing increased hypervascularity. In addition there appear to be more number of lesions with gross liver parenchymal heterogeneity. TECHNIQUE: Scan-Helical, Routine time = .6 secs. Rotation length - Full, Detector coverage = 40 mm, Helical thickness-5mm, Pitch and speed (mm/rot) .984:1/ 39.37, kV -120, mAs - modulated 120-600 (as per body thickness) contrast - Iomeron 400mg/dl.  
3B. FINDINGS: The portal-venous phase, contrast-enhanced axial CT image shows peripheral heterogenous contrast enhancement of the segment IV lesion (Black block arrow) and minimal peripheral as well as central enhancement of the caudate lobe lesion (black open arrow). TECHNIQUE: Scan-Helical, Routine time = 0.6 secs. Rotation length-Full, Detector coverage = 40 mm, Helical thickness-5mm, Pitch and speed (mm/rot) .984:1/ 39.37, kV -120, mAs - modulated 120-600 (as per body thickness) contrast -Iomeron 400mg/dl.  
3C. FINDINGS: The portal-venous phase, contrast-enhanced coronal multi planar reconstructed CT image shows heterogenous contrast enhancement of the segment IV lesion (Black block arrow). TECHNIQUE: Scan-Helical, Routine time = .6 secs. Rotation length - Full, Detector coverage = 40 mm, Helical thickness-5mm, Pitch and speed (mm/rot) .984:1/ 39.37, kV -120, mAs-modulated 120-600 (as per body thickness) contrast -iomeron 400mg/dl.  
3D. FINDINGS: The portal-venous phase, contrast-enhanced coronal multi planar reconstructed CT image shows multiple new enhancing lesions of varying sizes (black block arrows) studded in the entire liver parenchyma. TECHNIQUE: Scan-Helical, Routine time = .6 secs. Rotation length-Full, Detector coverage = 40 mm, Helical thickness - 5mm, Pitch and speed (mm/rot) .984:1/ 39.37, kV -120, mAs - modulated 120-600 (as per body thickness) contrast -iomeron 400mg/dl .





**Figure 4:** Histopathology findings of the biopsy obtained from liver lesions of 71-year-old man with hepatic angiosarcoma  
 4A. FINDINGS: sinusoidal and solid growth pattern of the cells with atrophic benign hepatocytes are seen. TECHNIQUE: Magnification X 100, HE  
 4B. FINDINGS: sinusoidal arrangement of atypical endothelial cells displaying irregular hyperchromatic nuclei. TECHNIQUE: Magnification X 200, HE  
 4C. FINDINGS: strong cd34 immunostaining of malignant endothelial cells, TECHNIQUE: at Magnification x 200, CD34 (labeled streptavidin-biotin (LSAB) technique) (biogenex, clone qbend/10, mouse species, labeled streptavidin-biotin (LSAB) Immunohistochemistry)

<b>Etiology</b>	<ul style="list-style-type: none"> <li>Primarily unknown</li> <li>Associated with Vinyl Chloride, thorium dioxide, arsenic and cyclophosphamide exposure</li> <li>Schistosoma Japonica infection, long-term use of androgenic-anabolic steroids</li> </ul>
<b>Incidence</b>	2% of Primary liver malignancies.
<b>Gender ratio</b>	Male : Female ratio = 3 : 1
<b>Age predilection</b>	50-79 years
<b>Risk factors</b>	<ul style="list-style-type: none"> <li>Carcinogens-as described in etiology</li> <li>Von Recklinghausen’s disease, hemochromatosis.</li> <li>Also seen in underlying liver cirrhosis</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>Surgical resection</li> <li>Chemotherapy</li> <li>Mostly radio resistant</li> </ul>
<b>Prognosis</b>	Poor. Survival 6 months - 2 years (with treatment)
<b>Imaging findings</b>	<ul style="list-style-type: none"> <li>Multiple nodules; hypoattenuating lesions, heterogeneous foci of enhancement less than aorta, no fixed pattern, ring enhancement in some nodules.</li> <li>Large solitary mass; heterogeneous and progressive enhancement</li> <li>Mixed pattern: Combined features of a) &amp; b) On CT and MRI- Imaging characteristics may parallel those of hemangioma / sometimes similar to hepatocellular carcinoma.</li> </ul>

**Table 1:** Summary table for hepatic angiosarcoma



	US	CT	MRI			Enhancement Pattern	PET	Scintigraphy
			T1	T2	DWI			
<b>Hemangioma</b>	<ul style="list-style-type: none"> <li>• Hyperechoic</li> <li>• Posterior acoustic enhancement</li> </ul>	<ul style="list-style-type: none"> <li>• Well demarcated</li> <li>• Central hypodensity</li> <li>• Peripheral nodular enhancement in 94%</li> </ul>	<ul style="list-style-type: none"> <li>• Iso-hypointense</li> <li>• Slightly higher than those of skeletal muscle</li> </ul>	<ul style="list-style-type: none"> <li>• Increasing hyperintensity with heavily weighted T2WI</li> <li>• Brighter than subcutaneous fat</li> </ul>	<ul style="list-style-type: none"> <li>• Hypointense</li> <li>• High ADC value, free diffusion</li> </ul>	<ul style="list-style-type: none"> <li>• Progressive, peripheral, discontinuous, contrast density like aorta at all phases.</li> </ul>	<ul style="list-style-type: none"> <li>• Accumulation present.</li> <li>• SUVs for FDG-PET = 0.7 - 1.67</li> </ul>	<ul style="list-style-type: none"> <li>• Tc<sup>99m</sup> pertechnetate RBC scan-decreased activity - early dynamic images, increased activity - delayed images, SPECT more sensitive.</li> </ul>
<b>HCC</b>	<ul style="list-style-type: none"> <li>• Heterogeneous echogenicity</li> <li>• Hypoechoic</li> </ul>	<ul style="list-style-type: none"> <li>• Heterogeneous hemorrhage</li> <li>• Central necrosis</li> </ul>	<ul style="list-style-type: none"> <li>• Iso, hypo or hyperintense depending on hemorrhagic contents</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperintense</li> </ul>	<ul style="list-style-type: none"> <li>• Restriction increases with increasing b values.</li> <li>• Low ADC</li> </ul>	<ul style="list-style-type: none"> <li>• Arterial hypervascularity with washout on delayed and equilibrium phases</li> </ul>	<ul style="list-style-type: none"> <li>• Low</li> <li>• Sensitivity for lesions &lt; or = 5 cm</li> <li>• No correlation with histologic grade.</li> <li>• Accurate for extrahepatic staging</li> </ul>	<ul style="list-style-type: none"> <li>• Triple tracer scintigraphy used.</li> </ul>
<b>Hepatic Angiosarcoma</b>	<ul style="list-style-type: none"> <li>• Multiple, heterogeneous echogenicity</li> <li>• predominantly hypoechoic lesions</li> </ul>	<ul style="list-style-type: none"> <li>• Hypoattenuated to liver</li> <li>• Often multiple</li> <li>• Commonly rupture into peritoneal cavity with hemoperitoneum.</li> </ul>	<ul style="list-style-type: none"> <li>• Iso, hypo or hyperintense depending on hemorrhagic contents</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperintense</li> </ul>	<ul style="list-style-type: none"> <li>• Restriction increases with higher B values, Low ADC</li> </ul>	<ul style="list-style-type: none"> <li>• Arterial hypervascularity with progressive enhancement</li> </ul>	<ul style="list-style-type: none"> <li>• FDG avid. used for distant metastases work up, not primary diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>• On RBC scintigraphy- No tracer uptake.</li> </ul>

**Table 2:** Differential diagnosis table for hepatic angiosarcoma

**ABBREVIATIONS**

- ADC - Apparent Diffusion coefficient
- CT - Computed tomography
- DW - Diffusion weighted
- DWI - Diffusion weighted imaging
- FDG PET - Fluorodeoxyglucose Positron emission tomography
- HCC - Hepatocellular carcinoma
- MRI - Magnetic resonance imaging
- PVP - Portal venous phase
- RBC - Red blood cell
- SPECT - Single-photon emission computed tomography
- SUV's - Standardized uptake values
- USG - Ultrasound

**KEYWORDS**

Angiosarcoma; Liver; MRI; CT; hepatocyte specific contrast

**ACKNOWLEDGEMENTS**

Rita Gulabani, Abhishek Anand and Dhananjay Singh for their technical expertise and radiographic skills

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