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Giant cavernous hemangioma of the liver with satellite nodules: Aspects on tumour / tissue interface: a case report

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Abstract

BACKGROUND

Background:

Giant hepatic cavernous hemangioma with multiple satellite nodules is a rare subtype of hepatic cavernous hemangioma, the most common vascular liver tumor. We report on a tumor with unusual histologic features: (A) finger-like infiltration pattern, (B) lack of encapsulation, (C) blurred tumor / liver interface, and (D) massive satellitosis—referring to the article "Hepatic cavernous hemangioma: underrecognized associated histologic features" by Kim *et al* (2005) in *Liver International*.

CASE SUMMARY

Case summary:

A 60-year-old man presented with increasing uncharacteristic abdominal discomfort and mildly elevated blood parameters of acute inflammation. Imaging revealed an unclear, giant liver tumor of the left liver lobe. A massive vascular tumor with extensive satellitosis broadly infiltrating the adjacent liver parenchyma was resected *via* hemihepatectomy of segments II / III. Histopathological diagnosis was giant hepatic cavernous hemangioma with multiple satellite nodules, featuring unusual characteristics hardly portrayed in the literature. Retrospectively, this particular

morphology can explain the difficult pre- and perioperative diagnosis of a vascular liver tumor that is usually readily identifiable by modern imaging methods.

CONCLUSION

Conclusion:

This case emphasizes the exact histological workup of tumor and tumor-induced parenchyma changes in radiologically unclassifiable liver tumors.

INTRODUCTION

Giant hepatic cavernous hemangioma with multiple satellite nodules is a rare subtype of hepatic cavernous hemangioma, the most common vascular liver tumor. We report on a tumor with unusual histologic features: (A) finger-like infiltration pattern, (B) lack of encapsulation, (C) blurred tumor / liver interface, and (D) massive satellitosis—referring to the article "Hepatic cavernous hemangioma: underrecognized associated histologic features" by Kim *et al* (2005) in *Liver International*.

CASE PRESENTATION

Chief complaints

Increasing abdominal pressure, finally emanating to the left thorax, indigestion, and night sweat over two months

History of present illness

Increasing abdominal pressure, finally emanating to the left thorax, indigestion, and night sweat over two months.

History of past illness

None.

Personal and family history

60-year-old man with an unclear liver tumor of the left liver lobe.

Physical examination

Symptoms comprised increasing abdominal pressure, finally emanating to the left thorax, indigestion, and night sweat over two months. Weight loss or exhaustion were not perceived.

Laboratory examinations

Leukocytes, GGT, and LDH were mildly elevated, liver enzymes in the normal range. CRP was mildly elevated at first but increased significantly with aggravation of symptoms.

Imaging examinations

Contrast enhanced CT showed a voluminous exophytic tumor arising from liver segment III, with atrophy of the left liver lobe, compression of the liver hilus and the left colon flexure

FINAL DIAGNOSIS

Giant hepatic vascular hemangioma with satellite nodules.

TREATMENT

Left lateral hemihepatectomy of segments II / III with construction of a bladder fistula was performed.

OUTCOME AND FOLLOW-UP

After resection the patient recovered well and was devoid of symptoms.

DISCUSSION

Hepatic cavernous hemangioma (CH) is a well-known entity, the most common benign vascular liver tumor with an incidence of 0.4 to 20% in autopsies[1–4]. The term "giant

cavernous hemangioma" should be applied for tumors greater than 4 cm[2,5,6], 5 cm[1,7], or even 10 cm[6], depending on the literature. It occurs more often and has greater dimensions in (young) women than in men[1–7]. Etiology and pathogenesis are still unknown, though hormonal influence is discussed as a possible trigger[1,2,7]. Some tumors express estrogen receptors, and growth during puberty, pregnancy, and under medication with oral contraceptives is observed[1,2,7,8–12]. However, single studies also negate a correlation between hormonal influence, sex, and tumor size[5]. A solitary lesion under 3 cm is typical, classically seen in the right posterior liver lobe[2,13], although tumors can occur anywhere in the liver[2,5,13]. In up to 10% of cases, multifocal tumors arise and seldom diffuse hemangiomatosis is found, both much more often in women than in men[1,2,5]. Rarely are hemangiomas associated with focal nodular hyperplasia (FNH)[2]. They are also observed in hereditary hemorrhagic telangiectasia (HHT; Rendu-Osler-Weber disease)[1,2].

Spontaneous involution by intratumoral thrombosis and vascular obliteration, as well as secondary fibrosis and calcification with phleboliths can occur[1,2,5,7], rarely resulting in a so-called "solitary necrotic nodule" as an end-stage form of completely sclerosed hemangioma[2]. Most tumors are asymptomatic and only detected by incidence. If the hemangioma lies directly under the liver capsule and starts to expand, capsule stretching can cause abdominal pain, and the tumor can even be palpable by clinical examination. Small CH only require surgery if symptomatic, extended tumors should be resected because of the elevated risk of rupture, acute thrombosis and tumor bleeding[1,2,7,14]. Alternatively, transarterial embolization or percutaneous radiofrequency ablation (RFA) can be an option[2]. Rarely is liver transplantation necessary[1,5]. A rare complication in giant hemangioma in the liver or in extremities is Kasabach Merritt syndrome[2,5], a form of disseminated intravascular coagulopathy (DIC) in convoluted tumor vessels with coagulopathy, thrombocythemia, and hypofibrinogenemia, triggered by intravascular aggregation of thrombocytes, strong activation of coagulation, and consumption of fibrinogen, with extensive bleeding.[15,16]

In most cases highly precise contrast enhanced ultrasound of the liver (CEUS) or contrast-enhanced CT or MRI imaging does not require histological confirmation of the diagnosis, sparing invasive liver biopsy with the risk of bleeding. Typical imaging reveals peripherical nodular enhancement in the arterial phase, resulting from tumor feeding *via* liver arteries, with progressive centripetal partial or complete fill-in in the portal venous phase, and washout in the late phase[17–19]. However, classical radio-morphological features can be lost with increasing tumor size and morphological variations like multinodularity[1,2,5] or rarely even liver infiltration, then referred to as diffuse hemangiomatosis[1]. Differential diagnosis of hepatic hemangiosarcoma (HHS) must be considered. Other (vascular) disorders like peliosis hepatis, Budd Chiari syndrome, or venous occlusive disease (VOD) / sinus obstruction syndrome (SOS) can mostly be excluded by anatomic distribution in the liver, lacking zonal growth and filling phenomenon[2].

Cavernous hemangioma endothelial cells, so-called "CHECs" by Zhang *et al* (2006), show an enhanced angiogenic activity compared with normal liver sinusoidal endothelial cells or "LSECs"[20]. They express elevated levels of vascular endothelial growth factor (VEGF), metalloproteinases, and angiopoietins[20,21]. The VEGF influence on vascular proliferation of liver hemangioma was also clinically noted. Shrinkage of incidentally detected liver hemangioma was observed during antiangiogenic therapy in patients with colon carcinoma who were treated with bevacicumab[22,23], a recombinant humanized monoclonal anti-VEGF-antibody hampering neoangiogenesis in various tumors or diabetic retinopathy. In hypoxic conditions, (neo)angiogenesis is promoted by autocrine and paracrine secretion of VEGF, which activates the PI3-Kinase / Akt-pathway and the Ras-dependent signaling pathway through MAP kinases ERK1 and ERK2. Hypoxia leads to ERK1 and ERK2 activation by phosphorylation, which then hamper degradation of hypoxia inducible factor 1α (HIF1α). This factor consecutively binds the hypoxia-responsible element of the VEGF promotor in the nucleus, enhancing VEGF expression, and resulting finally in the proliferation of endothelial cells[22,23]. Hu *et al* (2006) found an aberrantly enlarged endoplasmic reticulum (ER) in "CHECs" by

electron microscopy and a downregulation of the protein Derlin-1 that plays a role in the transport of misfolded proteins from the ER to the cytosol for degradation. A shrinkage of the ER to normal size again was observed when Derlin-1 was overexpressed[20], implying a possible error in protein degradation in consecutive storage in ER in "CHECs".

In our case, the tumor displayed massive satellitosis, but not the diffuse small cystic infiltration pattern of hemangiomatosis. Apart from the main tumor, we did not find the classical histomorphological criteria for CH ("well demarcated", "fibrous capsule-like border")[1,2,5,7] in the satellite nodules. However, we recognized several atypical features reported by Zimmermann *et al* (1996)[25] and Kim *et al* (2005)[5] in their series of giant cavernous liver hemangiomas with unusual features, like the so-described "interdigitating pattern"[25] where tumor parts have finger-like expansion into the liver parenchyma, without formation of a typical fibrous interface (Figure 2C−F). Considering these particular features, together with the classical morphology of the main tumor, other differential diagnosis like peliosis hepatis, hereditary hemorrhagic telangiectasia, or hemangiosarcoma could be readily excluded.

Spreading pattern also evoked the question of primarily multiple solitary hemangiomas in one liver lobe, of which one nodule started to expand massively, perhaps because of benefited localization next to greater arteria, or general arterial supply only sufficient for the expansion of one nodule. However, a review by Bioulac-Sage *et al* (2008) describes a similar extension pattern of dilatated vessels in the close periphery of giant hemangiomas (0.1−2.0 cm beyond tumor borders), so-called hemangioma-like vessels (HLV)[2], discussing the "HLVs" as a process of expansion. In our case, we found satellite nodules infiltrating the whole resected liver lobe, up to 10 cm away from the main tumor (Figure 1C, Table 1). The extremely low proliferation index and lack of TP53 accumulation in satellite nodules contradicted a rapid tumor expansion.

Blurred tumor borders and satellite nodules were a challenging aspect in preoperative imaging and, together with the untypical clinical setting (age, sex), did not permit a firm preoperative radiological diagnosis or definite exclusion of malignancy.

Hepatic cavernous hemangioma (CH) is a well-known entity, the most common benign vascular liver tumor with an incidence of 0.4 to 20% in autopsies[1–4]. The term "giant cavernous hemangioma" should be applied for tumors greater than 4 cm[2,5,6], 5 cm[1,7], or even 10 cm[6], depending on the literature. It occurs more often and has greater dimensions in (young) women than in men[1–7]. Etiology and pathogenesis are still unknown, though hormonal influence is discussed as a possible trigger[1,2,7]. Some tumors express estrogen receptors, and growth during puberty, pregnancy, and under medication with oral contraceptives is observed[1,2,7,8–12]. However, single studies also negate a correlation between hormonal influence, sex, and tumor size[5]. A solitary lesion under 3 cm is typical, classically seen in the right posterior liver lobe[2,13], although tumors can occur anywhere in the liver[2,5,13]. In up to 10% of cases, multifocal tumors arise and seldom diffuse hemangiomatosis is found, both much more often in women than in men[1,2,5]. Rarely are hemangiomas associated with focal nodular hyperplasia (FNH)[2]. They are also observed in hereditary hemorrhagic telangiectasia (HHT; Rendu-Osler-Weber disease)[1,2].

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CONCLUSION

Giant cavernous hemangioma of the liver with unusual features is a challenging preoperative diagnosis. It requires thorough combined radiological and histomorphological workup with special regard to (A) finger-like infiltration pattern, (B) lack of encapsulation, (C) blurred tumor / liver interface, and (D) massive satellitosis. Moreover, attention must be paid to areas with diffuse and dense vascular spreading pattern, so that hemangiomatosis is not overlooked. Considering these rarely described features is essential in preoperative imaging and liver biopsy, to not prematurely drop the diagnosis of cavernous hemangioma, as well as to enlarge the portfolio of (malignant) differential diagnosis. Cases like this enhance the importance of interdisciplinary collaboration of radiology, hepatology, and hepatopathology, and the correlation of rare histomorphological aspects with modern imaging methods.

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PRIMARY SOURCES

1	Ankang Wang, Jiaqi Deng, Baolin Qian, Hao Chen, Mingxing Li, Dayin Yang, Qiu Li, Zhengming Lei, Wenguang Fu. "Natural history of hepatic hemangioma: a follow-up analysis of 534 patients", Frontiers in Life Science, 2019 Crossref	36 words — 1%

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