Primary hepatic leiomyosarcoma (PHLS): A case report and literature review

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Abstract
We encountered a rare case of HLMS. US and plain CT showed ill-defined para-caval hepatic tumor in the caudate lobe. The contrast enhanced CT showed a relatively poorly enhanced tumor with non-enhanced area suggesting necrosis. On MRI, the tumor presented with low signal intensity on T1 in-phased image and heterogeneously high signal intensity on T2WI. On T1-opposed-phase, the tumor showed the slight elevation of the signal compared with T1 in -phased image. This phenomenon suggested shortening of T2* effects caused by faint hemorrhage. On dynamic enhanced MRI, the lesion showed gradually mild enhancement from the arterial to the venous phase with some necrotic area. By the CT-guided biopsy, the diagnosis of leiomyosarcoma with faint hemorrhage was made on immunohistochemical stain.

Keywords: Hepatic Leiomyosarcoma (HLMS) Intra-tumoral hemorrhage Opposed phase-MRI T1WI

Introduction
Hepatic leiomyosarcoma (HLMS) is an infrequent aggressive malignant tumor which usually presents para-IVC (Inferior vena cava) soft tissue tumor extending from the confluence of hepatic veins3). Usually conventional HLMSs are almost always metastatic, although EBV-associated LMS is known. These tumors showed low incidence in daily practice, they also occur at ligament teres besides para caval area. EBV virus was reported to be associated in the genesis especially in HIV patient or iatrogenic (usually organ transplantation associated) conditions. The diagnosis is often delayed until they reach a large size leading to dismal prognosis. We herein report a case of HLMS occurring in paracaval area. HLMS accounts for 3.6% (range: 0.9%–14%) of all liver malignancies [2]. The imaging findings of HLMS are often nonspecific and are not precisely differentiated from those of other benign and malignant hepatic tumors. Here, we describe the imaging findings of HLMS showing faint hemorrhage suspected by the high signal on T1-opposed-phased magnetic resonance imaging. Furthermore, we discuss the CT and MR imaging findings of HLMS in the past literature.

Case Report
A 86-year-old woman was referred to our hospital with chief complaining of abdominal pain with hypertension. She had no history of liver disease or alcohol abuse. Her past medical history and family history were unremarkable. Laboratory analysis revealed normal liver function tests including serum albumin level and prothrombin time. White blood cell count, platelet, α-fetoprotein, CA 19-9 and CEA, were also normal. Both antibody to hepatitis C virus and hepatitis B surface antigen were negative. The ICG clearance at 15 min was 12%. Abdominal ultrasonography revealed a para-caval hypoechoic area (Figure1a) which was gradually enhanced from arterial (Figure1b) to delayed portal venous phase (Figure1c) occupying the segments 1 ventral to IVC. The tumor encased IVC mildly. The border of the ventral limbs and head of rt. adrenal gland was obliterated in tumor. On MRI, the tumor exhibited hypo signal intensity on T1-in-phased weighted image (Figure2a) and a heterogeneously high signal intensity (Figure2b) on T2WI. IVC was mildly compressed and deformed.
On T1-opposed phase (Figure 2c), the several parts showed the elevation of signal suggesting faint hemorrhage or iron deposition. On dynamic Gd-DTPA enhanced MRI, the lesions showed gradual mild enhancement from the arterial to the venous phase with non-enhanced area suggesting necrosis. On DWI (diffusion weighted image), it showed heterogeneously high & low signal intensity with faint several intrahepatic metastatic tumors (Figure 3) as high signal intensity foci around the main tumor. Surgical exploration was not undertaken by her family desire, then the CT-guided-biopsy of the tumor from the dorsal part of the liver segment 1 was performed. On both CT and MRI, no apparent fat nor fibrous capsule were observed. The histopathological examination revealed non-epithelial mesenchymal tumor composed with spindle atypical cells intersecting each other (Figure 4a). On immunohistochemistry, SMA (smooth muscle actin: Figure 5) and desmin were positive, and they were negative for S-100, vimentin, NSE, calretinin, neurofilament, and CD34. Those findings confirmed the diagnosis of LMS (leiomyosarcoma).

Fig 1a, b, c: (a) Computed Tomography (CT) scan of the abdomen revealed an ill-defined soft tissue mass (arrows) in the caudate hepatic lobe partially en-circulating IVC. Dynamic CT scan of early arterial phase showed faint heterogeneous enhancement (b) and delayed portal venous phase (c) showed a persistently enhancing tumor measuring 5.2 \times 4.5 \times 3.8cm (arrows). The mass was thought to be a cholangiocarcinoma. Careful clinical and radiological examination did not reveal any other primary tumor site. IVC was deformed with mild compression and/or wall invasion by tumor. The border of the ventral limbs and head of rt. adrenal gland was obliterated.
Fig 2a, b, c: On MRI, the tumor presented with a low signal intensity on T1WI-in-phased weighted image (2a) and a heterogeneously high signal intensity (2b) on T2WI. IVC was slightly compressed and deformed. On T1-opposed-phased image (2c), the tumor showed the slight elevation of the signal suggesting faint hemorrhage. On dynamic Gd-DTPA enhanced MRI, the lesions showed gradual mild enhancement from the arterial to the venous phase with non-enhanced area suggesting necrosis (not shown).

Fig 3: On DWI (diffusion weighted image), it showed heterogeneously high & low signal intensity. It also showed faint intraparenchymal metastatic tumors as high signal intensity foci throughout all hepatic lobe. The low signal foci assumed to be caused by T2\textsuperscript{*} susceptibility effect of hemosiderin. Several faint intrahepatic metastatic foci were also revealed as high signal intensity foci. On both CT and MRI, no fat density nor apparent fibrous capsule were observed.

Fig 4: The histopathological examination suggested non-epithelial mesenchymal cells obtained by the cutaneous biopsy composed with spindle atypical tumors intersecting each other. Light microscopy demonstrated the typical growth pattern of LMS, that is, predominantly fascicular, with tumor bundles intersecting each other at wide angles and merging of tumor cells. Several mitoses and intratumoral faint hemorrhage (hematoma) were also present.
Discussion

The clinical manifestation of primary HLMS (hepatic leiomyosarcoma) is usually non-specific, such as abdominal pain, weight loss, vomiting and jaundice and/or hepatomegaly or a palpable mass on physical examination. Acute bleeding is a rare symptom in patients with HLMS [2]. Some patients may have abnormal liver function tests but essentially the α-fetoprotein and other serological markers are negative. The absence of serological markers and non-specific clinical manifestations often delay diagnosis. Histological pre-operative diagnosis of HLMS is controversial as with other liver tumors, because most of the tumors have propensity for tumor seeding along the needle track.

HLMS is a rare tumor that is difficult to diagnose clinically. Different primary hepatic sarcomas may have different clinical, morphologic, and radiological features. Sarcomas constitute only 1 to 2% of all primary malignant tumors of the liver with the majority being either hepatocellular carcinoma or cholangiocarcinoma. The two major primary sarcomas of the liver are angiosarcoma [3] and epithelioid hemangioendothelioma [4].

Other reported sarcomatous tumors occurring in the liver parenchyma are as follows: undifferentiated embryonal sarcoma (UES), fibrosarcoma, malignant fibrous histiocytoma (MFH), liposarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor (MPNST) and carcinosarcoma (including cystadenocarcinosarcoma). The other mesenchymal tumor are angiomylipoma, LCH (histiocytosis X) and solitary fibrous tumor, leiomyoma, lipoma, myelolipoma, pseudolipoma, myxoma, chondroma, and benign multicystic mesothelioma.

No underlying etiologic factors including hepatitis C virus are known. But concomitant association of trohotorastr, acquired immunodeficiency syndrome [5], Epstein-Barr virus [6] prior history of immunosuppression in post renal transplant were reported. The mean age of diagnosis is 52-58 years with sporadic occurrence of the tumor in the younger age group [7]. The laboratory data showed leukocytosis with elevation of CRP and hepatic enzyme, but rarely showed the elevation of tumor marker [8].

The mean survival time was less than 1 year in untreated patients, and the occurrence of metastasis is about 40% cases, and the reported mean size was 8.7 cm [12].

Macroscopically, leiomyosarcoma (LMS) often tended to degenerate. The necrosis and/or hemorrhage were commonly seen, therefore, cut-surface specimen exhibited pinkish white collar with yellowish area of necrosis or dark red hemorrhagic foci8. [10]. Microscopically, they are composed of intersecting bundles of elongated, spindle shaped cells and faint longitudinal striations. Nuclei are hyperchromatic and elongated. Mitotic activity is variable, typically less differentiated.

Immunohistochemical staining revealed that the tumor cells were positive for smooth muscle actin (SMA; Fig. 5) and desmin; by contrast, these tumor cells were negative for c-kit (CD117) suggesting gastrointestinal stromal tumors, human melanoma black 45 (HMB45), PNL2 and Ki-67. Demonstration of nuclear EBER is reported as more specific immunological tests [11]. In some cases, anti-viral treatment and restoration of immune response have resulted in tumor regression and long term survival. Histologically, smooth muscle tumors containing 5 or more mitoses per 50 –high-power fields are classified as malignant. The presence of necrosis is also strongly suggestive finding of malignancy. The pleomorphic LMS shows numerous pleomorphic giant cells intimately admixed with a component of more uniform appearing spindle and round neoplastic cells, bizarre mitotic figures and irregular zones of necrosis [17]. Our case was interpreted as conventional low grade LMS due to absence of necrosis and relative paucity of bizarre pleomorphic neoplastic cells. Typically the cut-surface showed uniform, gray-white color with streaks and strands and a whorled appearance in places. It might show areas of hemorrhage or necrosis.

Histological evaluation is indispensable not only for determining histological type but also for grading and predicting biological behavior. Conventional LMS invariably show reactivity for smooth muscle markers such as smooth muscle actin in 90 to 95 %, and desmin in 70-90% of the cases; HLMS carries a poor prognosis; with the longest disease free survival being 20 months. LMS of adrenal gland is one of exclusion and is based on radiological, biochemical, histomorphological and immunohistochemical evaluation. It carried a poor prognosis when morphologically they are large in size and histologically show lympho-vascular invasion and high grade nuclear features.
Although, the origin of tumor was indeterminate whether stem cells of liver parenchyma or smooth muscle cells of IVC wall, LMS usually arises from vessel wall (such as IVC or hepatic vein). Other mass invading IVC includes renal cell carcinoma, adrenal tumor such as adrenocortical carcinoma and HCC. The dynamic contrast enhanced CT pattern in previously reported cases was almost similar to that of cholangiocarcinoma, a hyperperfusional mass with a heterogeneous nature. Most hepatic leiomyosarcoma are metastatic tumors from other sites, such as soft tissue, gastrointestinal tract, uterus, retroperitoneum and lung. In retroperitoneal region, it is the second common tumor following after liposarcoma. So, exclusion of metastatic LMS is essential in making a diagnosis of primary hepatic LMS and multifocal lesions do not necessarily indicate metastasis.

In previously published cases of LMS, they also arose from smooth muscle cells of hepatic vein, bile ducts or ligamentum tere in addition to IVC. Tumor arising from the hepatic vein may develop Budd-Chiari syndrome and have a worse prognosis, while tumor arising from the ligamentum teres having a better prognosis due to its increased resectability [7]. On CT, a large, well-defined heterogeneous hypodense mass with internal and peripheral dominant enhancement or a cystic mass with an enhanced thickened wall and/or fibrous capsule were reported [13]. In the present case, the plain CT scan showed an ill-defined hypodensity mass adjacent to IVC in the caudate lobe of the liver. The border of the ventral limbs and head of rt. adrenal gland was obliterated. And then on CE-CT and MRI showed multiple satellite nodular lesions. On the basis of these imaging findings, highly or moderately differentiated hepatocellular carcinoma (HCC) and liver hemangioma were excluded. Therefore, practical imaging differential diagnosis were cholangiocellular carcinoma, poorly or undifferentiated HCC, combined or sclerotic HCC, metastatic tumors (metastatic MPNST, GIST and primary retroperitoneal sarcoma), and IVC-or adrenal origin LMS. Adrenal LMS is an extremely rare mesenchymal tumor which usually originates from the smooth muscle wall of the central adrenal vein and its branches [14]. Hepatic aden rest tumor (HART) is composed of low columnar or cuboidal clear cells, similar to adrenocortical tumor. At imaging, HART is typically demonstrating a hypervascular, round, well demarcated tumor was then subjected to CT phase with non gradual mild enhancement from the arterial to the venous phase. However, complete contrast-enhanced MRI, the masses were not evidently enhanced during the arterial phase. However, the masses were gradually enhanced through the portal phase to the 5-min delayed imaging. This result could be a characteristic MRI finding of HLMS [18]. In a previous report describing the DSA, no apparent tumor stain was found during the arterial and portal venous phases, whereas weak stain was detected during the delayed phase [16].

In the literature, they preferentially occur at para/intra-caval area [3, 6, 17] in the liver; and multiple satellite lesions were also observed in the remaining portion of the liver. PET-CT can be applied to sensitively detect primary tumors and metastases in which increased uptake of FDG [18]. The cause of HLMS is unknown, but hepatic smooth muscle cell tumors probably arise from hepatic vein, IVC, or bile ducts. Chronic hepatitis and cirrhosis are not causative factors because the rate of HLMS with cirrhosis is lower than that of HCC. LMS is generally larger and show more rapid growth than leiomyoma [18]. Some authors have suggested the presence of irregular margins, necrosis, and rapid growth as the most suggestive features of malignancy [19].

Diffusion-weighted imaging (DWI) has the potential to delineate malignant lesions as hyperintense areas with excellent tissue contrast, providing quantitative measurements of apparent diffusion coefficient (ADC) values. Tamai et al. [20] reported significant differences in mean ADC values of LMS compared with normal myometrium and degenerated leiomyomas, without any overlap. Namimoto et al. [21] showed that overlap in ADC values between leiomyosarcomas and ordinary leiomyomas (attributed to the “T2 blackout effect,” i.e., hypointensity on DWI caused by hypointensity on T2-weighted images) could be resolved with the evaluation of tumor-myometrium contrast ratio on T2-weighted images.

Thomassin-N et al. [22] reported that by combining the analysis of T2 signal intensity, b1000 images and ADC map, MRI achieved 92.4% accuracy in distinguishing benign and uncertain or malignant myometrial tumors. Generally, the mitotic index and number of mitoses are prognostic indicators for most non-epithelial malignant tumors. DWI shows an heterogeneously high signal suggesting mild cellularity showing proliferation of spindle-shaped cells with a high nucleus-to cytoplasm ratio. Nowadays, T1WI-IP and OP sequences are easily acquired during a standard protocol, using a dual gradient-echo technique with T1 weighting. Protocol for IP and OP MRI differs depending on the strength of the magnetic field: with a 1.5 T magnet, the interval on TE (time to echo) between IP and OP images are 4.6 and 2.3ms, respectively. When lipid and water exist simultaneously in a lesion, the result is a drop in signal on OP (opposed-phase) images when compared to IP images of the same lesion. Iron
storage causes significant local distortion of the nearby magnetic field, resulting in significant shortening of T2*. Therefore, hemochromatosis or hemosiderosis can be identified and characterized with a high level of confidence. In cases of iron storage disease, the hepatic parenchymal signal intensity increases on the image with T1WI-OP [24]. In our case, several parts showed the elevation of signal suggesting iron (hemosiderin) deposition such as old faint hemorrhage on T1WI-OP.

CT findings of HLMS have been described as a large, well-defined, heterogeneous-hypo density mass with internal and peripheral enhancement or cystic mass with an enhancing thick wall. Cystic variant of LMS may be misdiagnosed as hydatid cyst or liver abscess [25]. On MR imaging the tumor may display occasional encapsulation [26]. LMS grows slowly with no symptoms, but after it reached a certain size, it enlarges aggressively.

It often invades bile ducts, as well as the portal and hepatic veins. The lung was the most common metastatic site followed by the liver. The prognosis of patients in whom surgical resection was performed was relatively better than the un-operated cases. A total resection and optimal treatment of recurrence improved the prognosis [27] although 66% patients would have died without treatment. Due to the rarity of primary hepatic sarcoma, standard care of HLMS in particular, has not been defined. However surgical resection followed by adjuvant chemotherapy is being widely followed as an empirical manner [4, 5].

Resection surgery forms the cornerstone of successful management of HLMS with an intention of R0 resection. All patients with potentially resectable tumors with adequate remnant liver volume should undergo surgical exploration and liver resection. Criteria for inoperability would include extrahepatic tumor spread, diffuse intrahepatic tumor making the patient not a candidate for complete tumor removal, and impaired liver function precluding the planned hepatic resection. Liver transplant has been attempted sporadically in HLMS29.

Immune status manipulation may play an important role in prolonging survival in the post transplant period by preventing recurrence [30]. Although, LMS of the inferior vena cava extending into the hepatic veins and right atrium is described, radical surgical excision with reconstruction of the inferior vena cava by synthetic graft could be performed [31] if patient wants to be surgically managed.

In conclusion, in the present study, HLMS was found to be a hypovascular tumor, which showed poorly enhanced during the arterial and portal venous phases, heterogeneously enhanced during the delayed phase of enhanced CT/MRI. Intratumoral hemorrhage and necrosis were suggested by the findings of the slight elevation of signal on T1 opposed phase and non-enhanced foci on Gd-enhanced MRI. It was mainly located in the caudate hepatic lobe adjacent to IVC. We believe that these findings represented the imaging characteristics of HLMS.

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