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CASE REPORT

Metachronous Hepatic Angiosarcoma Presenting as a Mimic of Recurrent Hepatocellular Carcinoma

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Introduction

Primary hepatic angiosarcoma (PHA) is the third most common primary liver malignancy, after hepatocellular carcinoma and cholangiocarcinoma, accounting for 2% of primary liver malignancies and less than 1% of all sarcomas [1, 2]. PHA has been known to present in men over 60 years of age and has been associated with neurofibromatosis-1, anabolic steroids, hemochromatosis, vinyl chloride, thorotrast radiocontrast, and arsenic, although most cases are idiopathic [2, 3]. PHA is a very aggressive malignancy with a historical median survival of only 5 months despite treatment [4]. Our case highlights how this deadly disease can present as a mimic of recurrent hepatocellular carcinoma (HCC) in a patient with known prior HCC.

Case Report

The patient was a 62-year-old Hispanic male with a past medical history of hepatitis C-related liver cirrhosis treated with an interferon-based regimen. He was diagnosed with HCC via triphasic liver computed tomography (CT) showing a 2-cm hypervascular lesion in segment 8 (Fig. 1a) with subsequent venous washout (Fig. 1b). He was treated by transarterial chemoembolization (TACE) with doxorubicin and lipiodol contrast; post-TACE imaging showed good uptake of lipiodol (Fig. 1c), and his α-fetoprotein (AFP) dropped from 8.3 to 4 ng/mL. The patient was followed with imaging biannually with the last normal imaging up to 2 years post TACE (Fig. 2a). Repeat triphasic liver CT 3 months afterwards began to show a small hypodense focus superior to retained lipiodol in segment 8 which possibly represented necrosis (Fig. 2b). There was also a new arterial enhancement seen in adjacent segments without definitive washout on venous and delayed phase. His corresponding AFP was 2.8 ng/mL. Overall, it was thought that there were no hypervascular lesions to suggest recurrence of HCC.

Unfortunately, half a year later, the patient began having night sweats and intractable coughing. Multiple new lung nodules were found and triphasic liver CT showed a 9.1-cm mixed hypodense and arterially enhancing lesion in segment 8, and smaller lesions in adjacent segments (Fig. 3a), all with venous washout (Fig. 3b). AFP was noted to rise from 5 to 14 ng/mL. Overall, the clinical picture appeared consistent with metastatic HCC, and palliative TACE was given, with poor subsequent uptake of lipiodol in the tumor (Fig. 3c). Subsequently, the patient began to have shoulder pain and was found to have a lesion suspicious for osseous metastasis on nuclear bone scan. A core needle biopsy of the scapula revealed malignant angiosarcoma (Fig. 4a). A liver biopsy was obtained which was positive for CD31 (Fig. 4b), Fli1 (Fig. 4c), and D2-40, consistent with angiosarcoma. The patient was subsequently admitted for malignant spinal cord compression and was discharged on hospice given rapidly declining quality of life.

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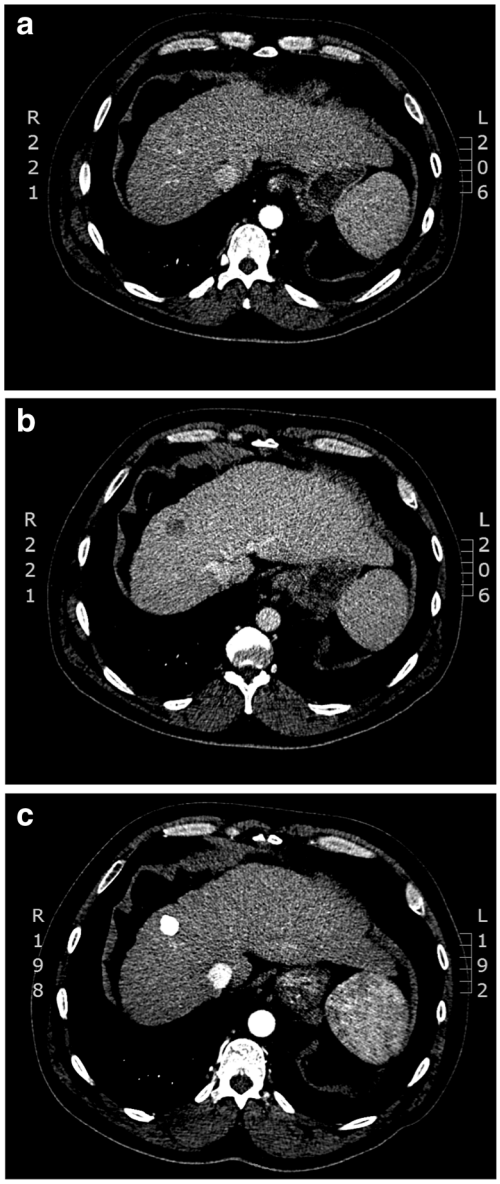

Fig. 1 Triphasic computed tomography (CT) scan of hepatocellular carcinoma (HCC). **a** CT Scan with single hypervascular lesion in segment 8, with **b** subsequent venous washout. **c** Imaging immediately post-TACE with good uptake of lipiodol

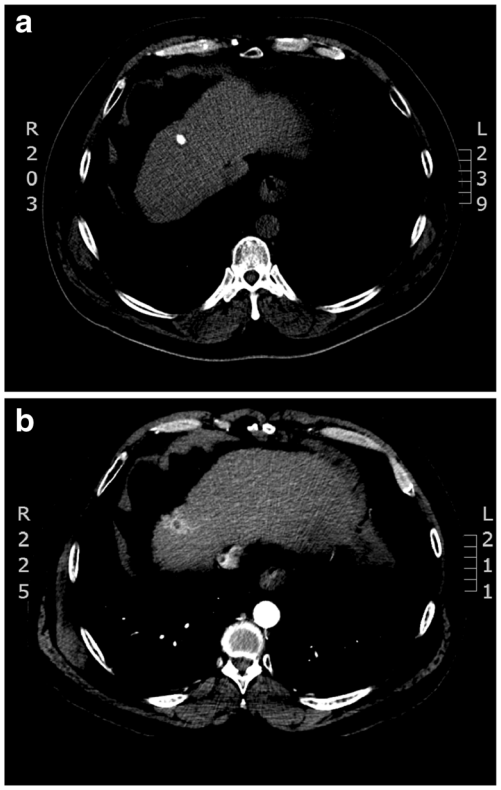

Fig. 2 **a** Follow up CT scan 2 years later with retained lipiodol and no evidence of recurrent tumor. **b** Three months later, small hypodense focus superior to retained lipiodol was discovered, possibly representing necrosis, and new arterial enhancement without definitive washout seen adjacent

Discussion

The diagnosis of primary hepatic angiosarcoma (PHA) may be suggested by triphasic CT scan in a patient with multiple hypoattenuating liver masses on arterial phase or as a heterogeneous dominant mass, especially when accompanied with the aforementioned risk factors [3, 5]. However, because PHA may have internal hemorrhage, it may mimic more common hypervascular lesions such as HCC, hypervascular metastases, or hemangioma by also presenting with arterial enhancement and heterogeneity [5]. It has been suggested that PHA can be distinguished from HCC as it will progressively enhance in the venous and delayed phase instead of exhibiting venous washout which is typical of HCC [5, 6]. To further distinguish the two, splenic metastases without either cirrhosis or elevated AFP may also suggest PHA instead of HCC [5, 7]. The diagnosis of PHA in this case was therefore unexpected given that patient's liver masses instead demonstrated arterial enhancement with subsequent venous washout similar to HCC and that the patient also had known history of cirrhosis, prior treated HCC, a rising AFP, and no known risk factors for PHA.

Although the standard for diagnosis of HCC is imaging-based, it is reasonable to question if the original diagnosis of HCC was correct given that no biopsy was done. First, however, one should remember that PHA is known to be a very aggressive malignancy. The 2-year symptom-free latency period without changes on serial imaging after treatment of the first lesion, followed by a rapid decline following the discovery of the second lesion is consistent with a metachronous, or subsequent, development of PHA. Second, the initial lesion had the classic appearance of HCC on imaging and had a lack of the arterial phase hypoattenuation which was prominent in the later PHA. Lastly, the patient's first and later tumor appeared to exhibit different uptake when exposed to lipiodol. Although excellent uptake of lipiodol was noted immediately post-TACE of the

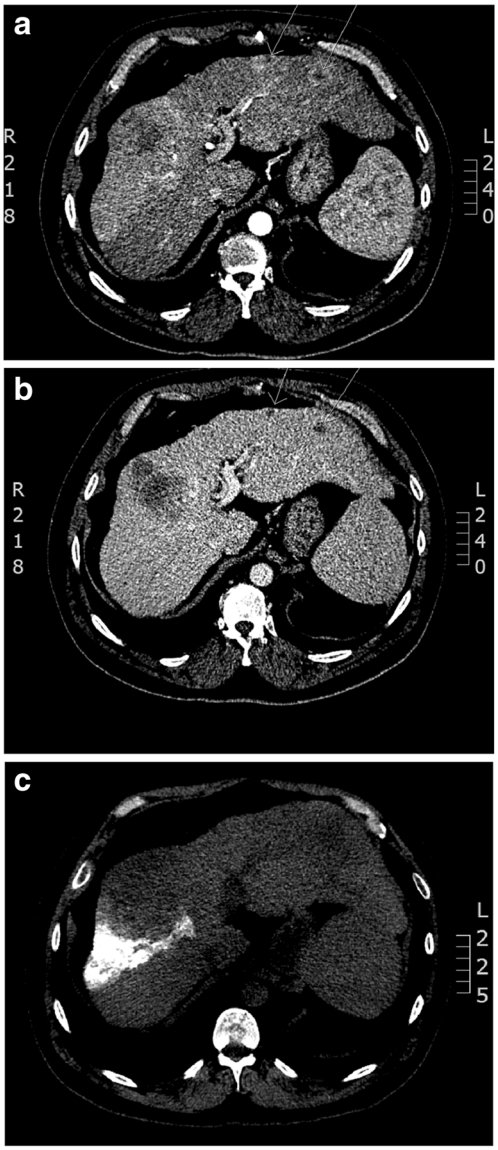

Fig. 3 **a** CT scan 6 months later with increased size of prior arterially enhancing lesion with new adjacent arterially enhancing lesions with central hypodensity (arrows) **b** and subsequent venous washout. **c** CT scan immediately post TACE treatment showing accumulation of lipiodol adjacent to large tumor in segment 8 with poor tumor uptake

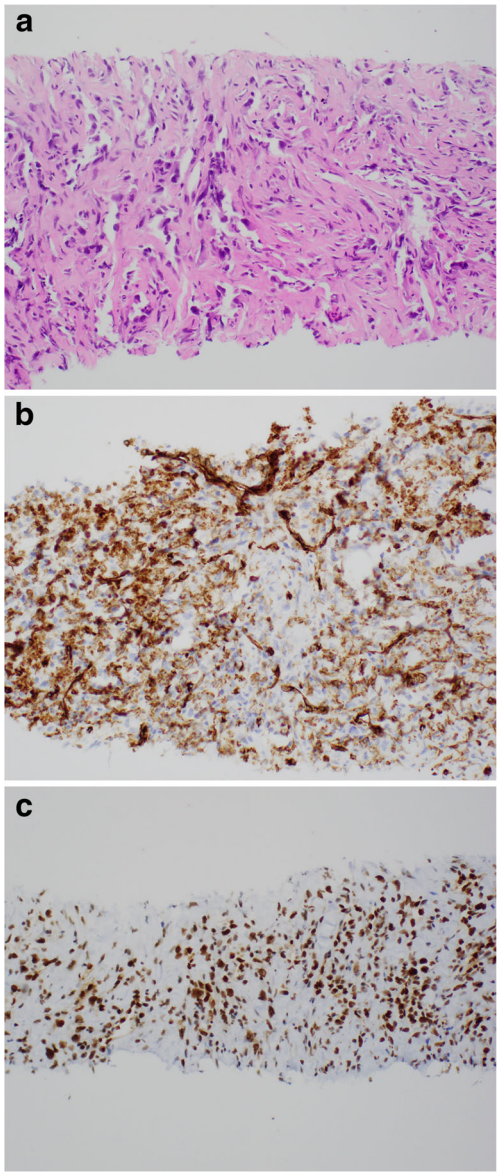

Fig. 4 **a** ×20: Atypical epithelioid cells with hyperchromatic chromatin and irregular nuclear contours surrounded by desmoplastic fibrous tissue. **b** ×20: CD31 focally staining a subset of tumor cells. **c** ×20: Fli-1 stain with diffuse strong positive nuclear staining in tumor cells

patient's initial tumor (Fig. 1c), after TACE of the second tumor, there was poor lipiodol uptake with mostly accumulation adjacent to the lesion (Fig. 3c). After TACE, HCC is known to exhibit excellent uptake of lipiodol in both the tumor and adjacent liver in the watershed of the hepatic artery branch infused. In contrast, the apparent lower affinity for lipiodol uptake in our case of hepatic angiosarcoma appears consistent with observations of partial uptake in other PHA cases in the literature [6], but this deserves further investigation in future studies.

PHA is a heterogenous disease with a histologically varied appearance—ranging from well-differentiated tumors with vascular differentiation to poorly differentiated non-vasoformative tumors. Other than histologic appearance, the diagnosis of PHA was evidenced by the presence of immunohistochemical markers—D2-40, CD31, and Fli-1. D2-40, a marker of lymphatic endothelial cells, stains 60% of cases [8]. Fli-1, a nuclear marker of endothelial differentiation, has been shown to have a sensitivity as high as 90% [9]. CD31, i.e., platelet endothelial cell adhesion molecule-1, is strongly expressed in angiosarcomas, ranging from ~ 80 to 100% depending on the location and/or degree of differentiation [10]. Taken together, the combination of histologic features and the results of immunohistochemical markers confirm the diagnosis of PHA.

Optimal management of PHA has not been established. Potentially curative resection should be considered for localized PHA, although only less than a quarter of patients are

typically without extrahepatic metastases at time of presentation [11]. Although some centers have reported dismal survival of up to 1 year despite complete resection, a recent single-center retrospective review from Taiwan has shown that resected solitary lesions followed by adjuvant systemic chemotherapy or directed therapy with TACE or transarterial embolization (TAE) can result in a median survival of up to 38 months after disease onset [2, 12, 13]. For unresectable cases, TACE has been incorporated into the management of PHA as a palliative measure with limited control rates, ranging from a quarter of a month to up to 12 months in the largest case series focusing on this topic [6]. PHA, similar to other soft tissue sarcomas, has been known to be poorly radiosensitive but there may be a palliative role [2]. Targeted therapies are of limited efficacy for angiosarcoma in general and include bevacizumab [14] and sorafenib [15]; however, these trials mostly did not include patients with PHA.

PHA and HCC occurring in the same patient is a rare phenomenon. Synchronous PHA and HCC have only been reported due to thorotrast radiocontrast [16] and vinyl chloride [17]. On the other hand, several studies have examined the risk of second or metachronous primary cancers in HCC patients with risk ranging from 2.8% [18] in population-based studies to 3.5% [19] in cohort studies among US patients. The most common metachronous cancers presenting after HCC were lung, prostate, hepatobiliary, and lymphoma [18]. To the best of our knowledge, PHA as a metachronous, second malignancy after HCC has not been described in a case report, cohort, or population-based study and this is the first known reported histologically confirmed case of PHA following HCC.

Conclusion

Our case illustrates that PHA can mimic other hypervascular lesions in the liver by presenting as multiple heterogeneous masses with enhanced arterial phase due to internal hemorrhages and may even demonstrate washout, similar to HCC. Clinicians should also recognize that PHA is on differential diagnosis at the time of HCC progression, especially when accompanied with metastases to unusual locations.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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