A Rare Case of Primary Sarcomatous Hepatocellular Carcinoma Without Previous Anticancer Therapy

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Primary sarcomatous hepatocellular carcinoma (PSHCC) is a rare and aggressive variety of hepatocellular carcinoma (HCC). The recent evidence suggests that anticancer therapy promotes the dedifferentiation of the carcinomatous component and is largely responsible for this aggressive variant of HCC. However, in the absence of any anticancer therapy, occurrence of PSHCC is extremely rare. Herein, we present a rare case report of a 65 year old male patient, with a hepatitis B positive status, presenting with PSHCC without any history of anticancer therapy. Detailed immunohistochemical evaluation of the tumor was performed with comparison of morphological and immunohistochemical features of the sarcomatous and carcinomatous components. This appears to be the first documented case of PSHCC from India, to the best of our knowledge. (J CLIN EXP HEPATOL 2017;7:378–384)

Primary sarcomatous hepatocellular carcinoma (PSHCC), also known as spindle cell carcinoma, carcinosarcoma or sarcomatoid carcinoma is an epithelial malignancy with divergent differentiation along the mesenchymal pathway due to dedifferentiation or epithelial-mesenchymal transition. The PSHCC is rare with an incidence of approximately 2% of all the hepatocellular carcinoma (HCCs). These tumors have an aggressive course due to their propensity for rapid growth, widespread metastases, infiltrating margins and frequent local recurrences. It has been postulated that the use of anticancer therapy including radiofrequency ablation, percutaneous ethanol injections and transarterial chemoembolisation (TACE) causes degeneration, necrosis and promote digression into sarcomatous phenotype. In addition, around 36% of HBV or HCV positive cases have been shown to be related to sarcomatous HCCs in the past 20 years in English literature.¹

A growing trend of PSHCC had been observed by Kojiro et al. due to an increase in the use of anticancer therapies in the previous years. There are only two cases of PSHCC reported in recent literature who did not receive any previous anticancer therapy. We report a case of a 65 year old male, hepatitis B positive status, who developed PSHCC

but had not received any anti-cancer therapy prior to the development of the neoplasm.

CASE REPORT

A 65 year old male patient presented with pain in the right upper quadrant of the abdomen for 7 months associated with loss of weight and appetite. The pain was dull aching with radiation toward the right shoulder. There was no history of fever, jaundice, melena, hematemesis, nausea, vomiting, constipation or diarrhea. The patient was a known smoker and alcoholic for last 35 years. The patient also had history of bronchial asthma and was on steroids via inhalational route. There was mild icterus although no pallor, clubbing, jaundice, cyanosis or lymphadenopathy was noted. On examination, there was tender hepatomegaly with the liver being palpable 5 cm below the right costal margin. There was no splenomegaly or any other visceromegaly. The contrast enhanced CT Scan (CECT) of the abdomen showed a large relatively well defined heterogeneously enhancing lesion involving segments 4/4b, 5 and 8 measuring 10.9 cm × 8.9 cm × 8.5 cm with peripheral enhancement in the arterial phase (Figure 1a). Radiologically, the lesion appeared to be a malignant vascular tumor versus a sarcoma. The liver function tests were deranged with mild unconjugated hyperbilirubinemia and rise in serum transaminase levels (total bilirubin 2.24 mg/dL, conjugated bilirubin 0.5 mg/dL, SGOT 650 U/L; SGPT 485 U/L, alkaline phosphatase 113 U/L) [normal cutoff of total bilirubin, SGOT, SGPT and alkaline phosphatase being 1.2 mg/dL, 35 U/L, 35 U/L and 128 U/L respectively]. The prothrombin time (PT) (12 s) and the international normalized ratio (INR) (1) was within normal range

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Abbreviations: PSHCC: primary sarcomatous hepatocellular carcinoma; HCC: hepatocellular carcinoma; TACE: transarterial chemoembolisation; CEA: carcinoembryonic antigen

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Figure 1 (a) Contrast enhanced CT scan showed a heterogeneously enhancing lesion. (b) Gross photograph of the cut surface of the enucleated tumor mass with tan color and areas of punctate hemorrhage and large area of central necrosis. (c) Gross photograph of the well circumscribed firm white nodules in a non-cirrhotic background. (d) The photomicrograph of the sarcomatous area showed partial encapsulation with spindle cells arranged in short fascicles (Hematoxylin and Eosin stain; 40 $\times$). (e) The spindle cells showed marked pleomorphism with scattered bizarre cells and a high mitotic activity (Hematoxylin and Eosin stain; 200 $\times$).

(12–14 s and <1.1 respectively). In addition, the patient was anemic having hemoglobin 8.8 g/dL. The HIV and HCV serology was non-reactive and echinococcus IgG was negative. The hepatitis B surface antigen (HBsAg) serology was reactive by ELISA and the hepatitis B viral load was $3 \times 10^6/\mu\text{L}$. The Serum alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels were within normal range (2 ng/mL and 0.4 ng/mL respectively) [normal cut-off of AFP and CEA being <10 ng/mL and <3 ng/mL respectively]. Clinically, the diagnostic possibility was HCC. However, TACE was not attempted as radiological possibility was not HCC and the lesion was operable. The patient underwent right lobectomy of the liver along with tumor enucleation and cholecystectomy.

Grossly, the main tumor mass measured 13 cm $\times$ 10 cm $\times$ 8 cm (enucleated tumor mass) (Figure 1b). Adjacent liver segment measured 9 cm $\times$ 9 cm $\times$ 4 cm and

showed multiple grayish white nodules, ranging from 0.4 cm to 1.8 cm in diameter. The enucleated tumor mass was grayish tan and showed a necrotic center with firm and solid areas at the periphery. Multiple hemorrhagic foci were also noted (Figure 1b) with focal whorled appearance. The smaller nodules were firm and fleshy and well circumscribed however, some of the smaller nodules had infiltrative margin and central necrotic areas. These nodules were seen dispersed all throughout the native liver parenchyma with capsular infiltration. The closest nodule was 1 cm away from the surgical resection limit. The native liver parenchyma was devoid of any cirrhotic nodule formation (Figure 1c).

The main tumor and the smaller nodules were meticulously sampled. Light microscopy revealed a multifocal tumor, composed of variably sized nodules punctuated by thick fibrous septa. The histomorphology of the

enucleated tumor mass and the smaller nodules vary. The enucleated tumor mass and some of the larger nodules were partly encapsulated and showed predominantly spindle cell morphology arranged in short interlacing fascicles and whorls with areas of diffuse sheet-like arrangement (Figure 1d). These spindle cells showed marked pleomorphism with scattered bizarre cells and tumor giant cells (Figure 1e). These cells had plump oval to elongated nuclei, blunt edges, vesicular chromatin, prominent nucleoli and moderate amount of wispy eosinophilic cytoplasm (Figure 1e). Only occasional cells showed epithelioid morphology. Mitotic figures were plenty including many atypical forms. Most of the smaller nodules were well-circumscribed and encapsulated. The tumor cells were disposed in nests and 4–7 cell thick trabeculae. These tumor cells were polygonal, hepatoid and were relatively monomorphic. They had centrally placed round to oval nuclei, vesicular chromatin, conspicuous to prominent nucleoli, well delineated cell membrane and moderate to

abundant amount of cytoplasm (Figure 2a and b). Kupffer cells were absent in these tumor nodules. Mitotic figures were scarce than the sarcomatous areas and atypical mitoses were not encountered. No hyaline globule, Mallory hyaline or bile was present. Only occasional nodule showed collision of the spindle-cell (sarcomatous) and the hepatoid (well differentiated) components, intermixing with each other, though sharply demarcated. At some places, the tumor cells with hepatoid morphology stayed as islands and nests within the sarcomatous tumor cells (Figure 2c). However, the gross morphology of these nodules was indistinguishable from the rest. An inflammatory component comprising of lymphocytes was seen within the tumor as a result of adjacent necrosis as well as a component of tumor-infiltrating lymphocytes. There was no hematopoietic focus. Reticulin stain showed the hepatoid area to be reticulin-poor whereas the sarcomatous area was reticulin-rich, and both these areas showed loss of normal reticulin framework (Figure 2d). No altered

Figure 2 (a) The photomicrograph of the nodule showing well differentiated hepatocellular carcinoma morphology in a non-cirrhotic background (Hematoxylin and Eosin stain; 40 $\times$). (b) The tumor cells were arranged in the form of nests and 4–7 cell layer thick trabeculae and were hepatoid (Hematoxylin and Eosin stain; 200 $\times$). (c) The photomicrograph of the nodule showing collision of the sarcomatous and well-differentiated hepatocellular carcinoma morphology with nests and islands of hepatocellular carcinoma surrounded by spindle cells (Hematoxylin and Eosin stain; 200 $\times$). (d) The reticulin stain showed loss of reticulin in the well-differentiated hepatocellular carcinoma component whereas the sarcomatous component was reticulin-rich (Reticulin stain; 400 $\times$).

Figure 3 The comparison between the immunohistochemistry pattern of the well differentiated and the sarcomatous areas; Granular cytoplasmic arginase positivity in the well differentiated component and paranuclear globules in the sarcomatous component (a) (Arginase IHC, 200×); Strong cytoplasmic positivity for Heppar-1 (b) and Glypican-3 (c) in the well differentiated component and negativity in the sarcomatous component (Heppar-1 and Glypican-3 IHC, 200×); Strong diffuse cytoplasmic vimentin positivity in the sarcomatous component and negativity in the well differentiated component (d) (Vimentin IHC, 200×); Strong diffuse nuclear p53 positivity in the sarcomatous component with occasional faint positivity in the well differentiated component (e) (p53 IHC, 200×); Strong granular cytoplasmic HBsAg positivity in the benign hepatocytes (f) (HBsAg IHC, 400×).

foci of hepatocytes were noted on performing Periodic acid Schiff (PAS) and Perl's stain. Large areas of necrosis with perivascular preservation of the tumor cells were noted.

On immunohistochemistry (IHC), the areas with hepatoid morphology showed diffuse granular cytoplasmic positivity for arginase immunostain, whereas, the arginase positivity was restricted to paranuclear location as globules in the sarcomatous areas (Figure 3a). The intensity of the arginase positivity was much more in the hepatoid areas as compared to the sarcomatous areas. Hepatocyte paraffin antibody (Heppar1) showed intense, diffuse granular cytoplasmic positivity in the hepatoid areas whereas negative in the sarcomatous areas (Figure 3b). Similarly, glypican 3 was positive (strong cytoplasmic granular) in the hepatoid areas and negative in the sarcomatous areas (Figure 3c). In contrast, vimentin showed intense diffuse cytoplasmic positivity in the sarcomatous component and negativity in the hepatoid component (Figure 3d). The CK8/18 showed variable patchy positivity in the hepatoid component, though the sarcomatous component was negative for it. IHC for p53 showed strong diffuse nuclear positivity in the sarcomatous component and variable focal nuclear positivity in the hepatoid component (Figure 3e). Importantly, the well differentiated hepatocellular component showed negativity for p53, and the more poorly differentiated areas showed increased p53 positivity. The CD34

immunostain showed different vascular pattern in the hepatoid and sarcomatous areas, the sarcomatous component having more vascular density and haphazard pattern. CK7, CD56, CD68, CD117, AFP (alpha-fetoprotein), SMA (smooth muscle actin), desmin and synaptophysin were negative in both these components. HBsAg showed granular cytoplasmic and paranuclear positivity of variable intensity in the benign hepatocytes in a patchy distribution (Figure 3f). Very occasional tumor cells with hepatoid morphology also showed faint cytoplasmic positivity. IHC for HBcAg highlighted occasional nucleus of the benign hepatocytes only. The sarcomatous component was devoid of any HBsAg or HBcAg positivity. The histomorphological, tinctorial and immunohistochemical characters of the hepatoid and sarcomatous components as compared to the native liver parenchyma is depicted in Table 1.

The adjoining non-tumorous liver parenchyma showed maintained lobular architecture with stage 3 fibrosis in the portal tracts and dense lymphomononuclear inflammatory infiltrate (score 4) with minimal interface hepatitis (score 1). Lobular inflammation was seen in approximately 2–4 foci per 10× field (score 2). No focus of confluent hepatic necrosis was noted (score 0). No evidence of steatosis, ductal damage, ductopenia, pericellular fibrosis, Mallory hyaline, perivenular sclerosis or neutrophilic satellitosis was noted to suggest a coexisting alcoholic liver

Table 1 Table for Comparing the Morphology, Special Stains and Immunohistochemical Profile of the Benign, Well-moderately Differentiated Malignant Hepatocellular and Sarcomatous Components.

	Native liver parenchyma	Well/moderately differentiated HCC component	Primary sarcomatous HCC component
Histomorphology	Maintained cord pattern	Loss of cord pattern (>2 cell layer thick cords), other patterns (pseudoacinar, solid, etc.)	Diffuse sheet and fascicular arrangement
Cytomorphology	Hepatoid cell with bland nuclear chromatin	Hepatoid cells (polygonal) to few bizarre cells and prominent/macronucleoli	Spindle cell morphology with/without nucleoli
Heterologous element	Absent	Usually absent	May be present (absent in this study)
Reticulin stain	Maintained reticulin pattern	Loss of reticulin	Reticulin-rich like any other sarcoma; normal reticulin pattern of liver is lost
Per-iodic acid Schiff (PAS) stain	Normal glycogen content; No hyaline globules	Loss of glycogen may be seen; Hyaline globules $\pm$ (absent in this study)	No PAS positive granules in the tumor cells; Usually no hyaline globules (absent in this study)
Perls' stain	No/mild Perls' positive granules (absent in this study)	Perls' granules may be absent (absent in this study)	No Perls' positive granules
Heppar-1	3+ diffuse granular cytoplasmic	1 $\pm$ 2+ diffuse granular cytoplasmic	Negative
Glypican 3	Negative	3+ diffuse cytoplasmic granular	Negative
Arginase	3+ diffuse granular cytoplasmic	2 $\pm$ 3+ diffuse granular cytoplasmic	1 $\pm$ 2+ paranuclear globular
CK8/18	3+ diffuse membranocyttoplasmic positivity	1 $\pm$ 2+ patchy positivity (may be strong positive)	Negative
CK7	3+ membranous positivity in the ducts	Negative	Negative
CD34	Negative in the sinusoids	Positive around hepatocytes	Different vascular pattern
p53	Negative	1 $\pm$ 2+ nuclear patchy	3+ diffuse nuclear
Vimentin	Negative	Negative	3+ diffuse cytoplasmic
CD56	Negative	Negative	Negative
CD68	Negative	Negative	Negative
AFP (alpha-fetoprotein)	Negative	Negative (may be positive)	Negative
SMA (smooth muscle actin)	Negative	Negative	Negative (may be positive)
Desmin	Negative	Negative	Negative (may be positive)
HBsAg (in positive cases)	3+ patchy/diffuse granular cytoplasmic, paranuclear and membranous	1 $\pm$ 2+ very patchy/occasional cells (Index case)/negative	Negative

HCC: hepatocellular carcinoma.

disease. No dysplastic nodule was seen in this adjacent liver parenchyma.

Based on the morphology and IHC, a diagnosis of sarcomatous HCC coexisting with well-differentiated HCC in a background of Hepatitis B virus related chronic hepatitis (necroinflammatory score, Ishak = 7, stage 3 fibrosis) was rendered.

DISCUSSION

PSHCC is a rare aggressive primary malignancy of the liver, the estimated incidence being approximately 2% in surgical specimen and 3.9–9.4% of all HCCs in two large Japanese autopsy studies conducted in the late 1980s.^{2–4} These

studies also highlighted the rise in the incidence of PSHCC due to the advent of the anticancer therapies. In contrast to these large Japanese studies and a few Korean and Chinese studies, the estimated incidence of PSHCC in the Western literature is even lower, being restricted to occasional case reports and small case series.¹ There are only a few cases of PSHCC without prior anticancer therapy that exist in the English literature. We also report a rare case of PSHCC without previous anticancer therapy with detailed immunohistochemical analysis.

The PSHCC is known under different rubrics including sarcomatoid carcinoma, carcinosarcoma, HCC with sarcomatous change, spindle cell carcinoma or pseudosarcoma. However, some people reserve the term “carcinosarcoma”

for those with malignant heterologous element.⁵ Both these malignancies are equally aggressive with a median survival period of 6–10 months.⁵ The etiology of PSHCC remains elusive till date though anticancer drugs have been implicated in the past.⁴ Viral infection including chronic hepatitis B as well as hepatitis C infection is commonly associated with PSHCC^{1,5} as was found in the index patient. The sarcomatous component is considered to be dedifferentiated carcinoma component and is found to be intricately admixed with a carcinoma component.^{1,2} This carcinoma component is commonly HCC, as in this case or rarely could be cholangiocarcinoma.^{1,5} Moreover, in some cases, the HCC or cholangiocarcinoma components may separately coexist.^{6–8} Anticancer drugs are known to cause degenerative changes in the HCC or the carcinomatous component, promoting their dedifferentiation. Hence, in most of the cases, the PSHCC arises after radio-frequency ablation, percutaneous ethanol injection and transarterial chemoembolization (TACE).^{2,4} The occurrence of PSHCC without any previous anticancer therapy is rare with only occasional case reports in the literature.^{2,4,9,10}

Clinically, the patients of PSHCC are elderly male and present with large mass. Viral marker positivity in the serum, alcohol ingestion and history of previous therapies are commonly associated with PSHCC which was also seen in our patient. The serum AFP level in majority of the cases is not elevated as found in this index patient too. However, most of PSHCC had history of previous anticancer therapy which was absent in our patient.

The pathogenesis of PSHCC remains elusive. Some researchers consider it to be a collision tumor of a sarcoma and a HCC whereas others believe it to be originated from dedifferentiated HCC.^{2,11} The proponents of the second theory consider chemotherapeutic agents to promote necrosis and dedifferentiation. The former theory could be true in sporadic cases like ours although no substantial proof is available. However, in this index case also, arginase positivity in the spindle cell component speaks volumes about the primary hepatocellular origin of the spindle cells, arginase being a highly specific marker of hepatocyte differentiation. This also necessarily supports the dedifferentiation theory rather than the theory of collision. Although no chemotherapeutic agent is implicated in the index case, the arginase positivity supports the dedifferentiation theory strongly and needs to be further probed into. There was no evidence of any chemotherapy in this index case. However, the presence of multiple etiologies like the hepatitis B virus and the history of alcohol ingestion appear to affect the occurrence of PSHCC in a genetically susceptible individual. Moreover, the occurrence of PSHCC is extremely rare in Indian population and this case appears to be the first documented case of PSHCC from India. It appears that ethnicity also plays a major role in the occurrence of this tumor.

Morphologically, the tumor is characterized by spindle cells in different arrangements with areas of necrosis and

hemorrhage and with or without any heterologous element. Pure sarcomatous carcinoma is extremely rare and commonly the carcinomatous focus is identified admixed with the sarcomatous component or separately. The carcinomatous focus can be HCC or less commonly cholangiocarcinoma. The immunohistochemical features of the sarcomatous and the carcinomatous components differ with diffuse bright expression of vimentin in the sarcomatous and Heppar-1 in the HCC component. Although previous studies have found CK 8/18 to be focally positive in the sarcomatous component, it was absent in our case. None of the previous studies have demonstrated the role of arginase, a new, novel, highly sensitive and specific marker of hepatocellular differentiation.¹² We observed arginase positivity in both the HCC as well the sarcomatous component, ruling out the possibility of a primary sarcoma coexisting with HCC, as already discussed. The p53 is over expressed in most malignant tumors but has been reported in a few cases of PSHCC.¹⁰ Diffuse p53 expression was limited to the sarcomatous component in the index case and was focal in the HCC areas and least in more well-differentiated areas. This finding probably highlights the fact that sarcomatous dedifferentiation in HCC could be a result of cumulative mutation of which p53 plays a significant role.

PSHCC needs to be distinguished from other tumors due to its highly aggressive behavior. The differential in PSHCC depends upon the area of sampling as the proportion of the sarcomatous and hepatocellular areas vary in a given tumor. Different primary sarcomas of the liver including angiosarcoma should be considered in the differential if no hepatocellular area is found. However, a negative CD31 and CD34 staining will help to refute the diagnosis of angiosarcoma. Similarly, other malignant mesenchymal tumors including leiomyosarcoma, rhabdomyosarcoma or undifferentiated sarcoma can be ruled out by necessary IHC for lineage differentiation. It is necessary to remember, that heterologous components can be present in PSHCC and can be the only area sampled in a small biopsy. Arginase positivity will be helpful in such cases where only the mesenchymal areas have been sampled. A diagnosis of solitary fibrous tumor can easily be refuted due to the lack of the morphological pattern and negative CD34 stain. Similarly, IgG4 related disease can also be easily negated due to the lack of the inflammatory component in PSHCC and the presence of significant atypia. Above all, arginase positivity definitely highlights its hepatocellular origin and irrespective of hepatocellular area sampled, a possibility of PSHCC can be considered based on the arginase positivity.

CONCLUSION

This case report demonstrates a rare variant of HCC, known as PSHCC not arising in a background of anticancer therapy. Though rare, this variant can also occur

without any previous anti-cancer therapy especially if the viral serology is positive. Hence morphological alterations both gross and microscopic are essential for accurate diagnosis. The IHC is a useful adjunct to differentiate it from other type of sarcomas. Arginase is a useful enzyme and highlights the spindle cell component of hepatocellular in origin, though its role needs to be further elucidated in PSHCC which has aggressive clinical behavior.

CONFLICTS OF INTEREST

The authors have none to declare.

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