

CASE REPORT

Oesophageal hepatoid carcinoma with liver metastasis, a diagnostic dilemma

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Abstract

Alpha-fetoprotein (AFP)-producing carcinoma which microscopically mimics hepatocellular carcinoma (HCC) is a rare entity known as hepatoid adenocarcinoma (HC). They usually arise in the stomach, while oesophageal origin is only occasionally encountered. This tumour is highly aggressive and is associated with a poor prognosis. They frequently metastasise to the liver, thus giving rise to diagnostic difficulty, especially in cases where simultaneous oesophageal and liver mass are present. We reported a case of oesophageal hepatoid carcinoma with multiple liver metastasis, that was associated with an increased serum AFP. The distinction between HCC and HC is important because HC is more aggressive and has a poorer prognosis with limited therapeutic options. An extensive diagnostic work-up which include a thorough clinical history, radiological investigations (computed tomography or magnetic resonance imaging) as well as tissue biopsy supported by a panel of immunohistochemical markers are necessary to aid in the diagnosis of HC.

Keywords: Hepatoid carcinoma, oesophageal cancer, alpha-fetoprotein, hepatocellular carcinoma

INTRODUCTION

Upper gastrointestinal tract malignancies that exhibit hepatoid differentiation, also known as hepatoid carcinoma (HC) are rarely encountered. Morphologically, they mimic hepatocellular carcinoma (HCC) and are associated with elevated serum alpha-fetoprotein (AFP), hence they are also known as AFP-producing carcinoma. AFP-producing carcinoma was first reported in the literature in 1970 and the common site of origin is the stomach.¹ Primary oesophageal HC is rarely described in the literature. Therefore, when there are liver and oesophageal tumour present synchronously, a metastatic HCC has to be excluded. However, the differentiation between these two entities may not be so straightforward. An extensive diagnostic work-up for the primary origin is necessary, as HC is more aggressive with limited therapeutic options. Here we present an interesting case of oesophageal HC with multiple liver metastases which resemble HCC in the initial presentation.

CASE REPORT

A 25-year-old Malay man with no known medical

illness, presented to our Emergency Department with epigastric pain, obstructive jaundice, loss of weight and loss of appetite. Two months prior, he was admitted into a private hospital for treatment of leptospirosis. He had a computed tomography (CT) scan conducted there and it showed presence of a large liver mass with intrahepatic metastasis and lymphadenopathy. However, he defaulted follow up at the private hospital.

Upon admission to our institution, he had laboratory investigations carried out which showed impaired liver functions with elevated bilirubin (101.2 mmol/L), alkaline phosphatase (ALP) of 699 U/L and alanine aminotransferase (ALT) of 234 U/L, with reduced albumin (28 g/L). Serum tumour markers showed a raised AFP level (1499 ng/mL) and CA19-9 (100 U/ml) with a normal carcinoembryonic antigen (CEA) level. His haemoglobin level was also low (9.6 g/dL). Viral serology screening for Hepatitis B and C was negative.

In view of the liver mass seen in the initial CT scan, a contrast-enhanced CT scan of thorax, abdomen and pelvis was repeated. The

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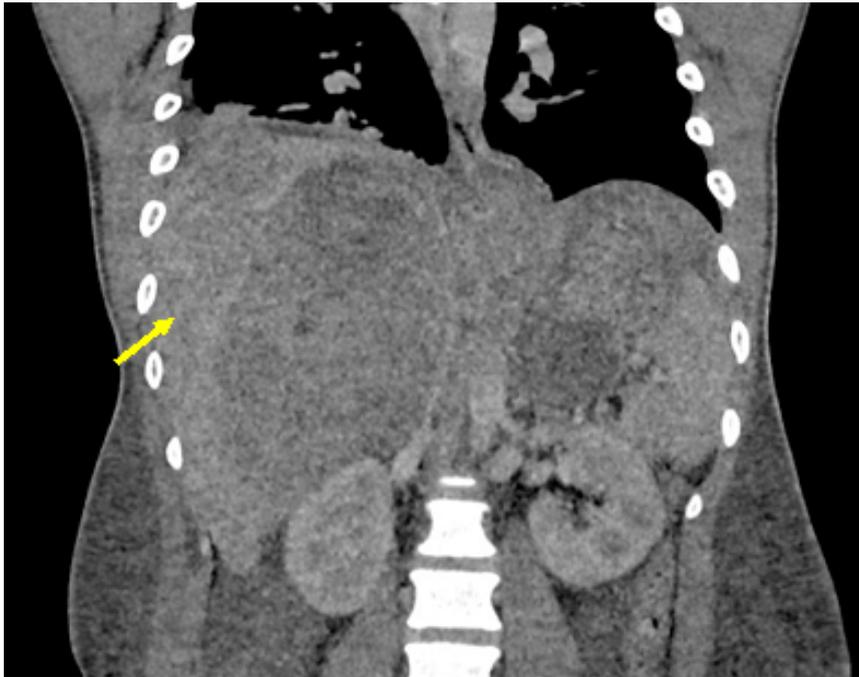


FIG. 1: Contrast-enhanced CT scan of the abdomen in coronal plane showed a large hypodense mass occupying the right lobe of the liver (arrow).

scan showed presence of a huge mass at right lobe of liver measuring 17.8 x 15.3 x 16.3 cm with necrotic centre, portal vein thrombosis, as well as left intrahepatic ducts dilatation and lymphadenopathy at portal region. The findings were suggestive of hepatocellular

carcinoma (HCC) with nodal metastasis (Fig.1). There was another intraluminal hypodense mass measuring 3.7 x 3.2 x 3.3 cm seen at the gastroesophageal junction (Fig. 2). Consequently, an oesophagogastroduodenoscopy (OGDS) was performed which revealed a large,



FIG. 2: CT scan in axial section revealed an eccentric mass within the lower oesophagus with luminal narrowing (arrow). Note the mass within the liver and presence of right pleural effusion.

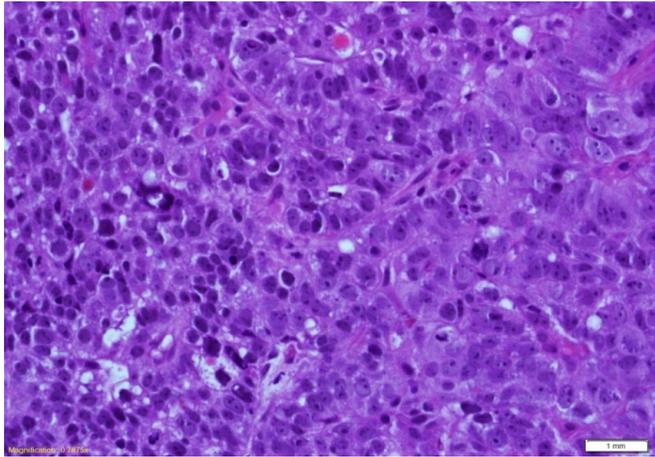


FIG. 3: Malignant cells were large, polygonal cells showing large, pleomorphic nuclei with occasional prominent nucleoli. They were arranged in trabecular, cords and with some vague glandular formation (H&E, x400).

obstructive polypoidal mucosal mass at the lower oesophagus. A biopsy of the oesophageal mass was taken.

Histopathological examination of the mass showed a poorly differentiated, pleomorphic, malignant cells infiltration with hepatoid features, arranged in trabecular, cords and vague glandular formation. The malignant cells display irregular, hyperchromatic to vesicular nuclei, multiple prominent nucleoli and moderate

cytoplasm with some scattered intracytoplasmic eosinophilic hyaline droplets seen (Fig. 3).

Immunohistochemical study was then performed to establish the primary origin of the malignant cells. The cells showed strong positivity for Glypican3, cytokeratin 19 (CK19) and CK AE1/AE3. They are negative for HepPar-1, AFP, CEA, CK7 and CK20 (Fig. 4). Special stain with periodic acid-Schiff (PAS) with and without diastase showed

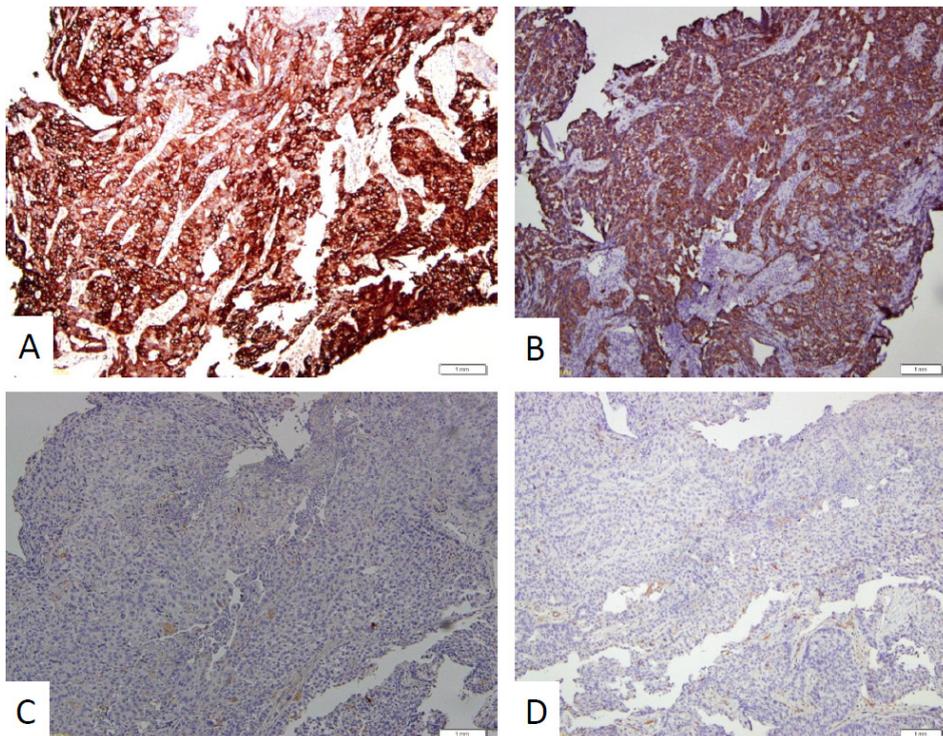


FIG. 4: The malignant cells were strongly positive for Glypican-3 (A) and CK19 (B). They were negative toward AFP (C) and Hep Par-1 (D) (IHC, x200).

presence of cytoplasmic glycogen and scattered intracytoplasmic hyaline globules. Therefore, morphology and immunohistochemical profile of the specimen were in keeping with primary oesophageal hepatoid carcinoma, with presence of extensive liver metastasis. With stage IV tumour and worsening condition of the patient, surgery was deemed unsuitable. The patient was referred for palliative care support.

DISCUSSION

HC is a rare type of extrahepatic carcinoma, with clinical presentations and cytomorphology that mimics HCC, leading to challenges in making an accurate diagnosis. In 1970, Bourreille *et al.* first reported a case of gastric carcinoma with synchronous liver metastasis and an increase in serum AFP, leading to the concept of AFP-positive gastric cancer.¹ This tumour is also called HC due to its morphological resemblance to hepatocytes as well as its association with high AFP level.^{2,3} The incidence is between 1.3% to 15% worldwide.⁴ In terms of location, more than 80% of HC arises from the stomach, followed by other sites like gallbladder, uterus, lung and urinary bladder. Only rarely do they originate from the oesophagus and peritoneum, which accounts for less than 1% of cases.⁴ In our case, the tumour arose from the oesophagus with multiple metastases to the liver.

Patients with HC are usually male, with age ranging from 32 to 87 years old with typical increase in serum AFP level up to 6400 ng/mL in more than 85% of cases.^{4,11} In general, AFP-producing tumours are usually related with poor prognosis and advanced stage at diagnosis. Previous studies have reported that these tumours demonstrated the following characteristics of an aggressive tumour i.e frequent liver and nodal metastasis, stronger proliferation, higher apoptotic rate and more neovascularisation with short survival time.^{4,5} A study by Su *et al.* showed only 12 months median survival for HC, with more than 50% of patients died within the first 12 months of diagnosis.⁴

HC resemble HCC both clinically and morphologically. The difficulty in differentiating these two entities arises especially when there are concurrent liver and gastrointestinal tumours present in a patient. In our case, the tumour within the liver was huge (17 cm), and the CT scan was suggestive of HCC, thus the tumour within the oesophagus could have been a metastatic focus. Although uncommon, there

are reported cases showing HCC metastasis to extrahepatic sites such as the lung, lymph nodes, adrenal and rarely to the gastrointestinal tract and the oesophagus.^{6,7,16} In endemic HCC areas with the highest reported rates of Hepatitis B virus infection (such as in Southeast Asia and sub-Saharan Africa), HC may also be incorrectly diagnosed as HCC.⁸ Our patient however lacked any possible risk factors for developing HCC i.e liver cirrhosis, Hepatitis B or C viral infection, chronic alcoholism or other liver diseases such as haemochromatosis, autoimmune hepatitis or Wilson's disease.⁸ HCC is also rare before the age of 40 and reaches a peak at approximately 70 years of age.⁸ Therefore, the absence of clinical risk factors in our patient are the points against diagnosis of HCC. An accurate diagnosis of HC and HCC is crucial as they differ in treatment options and prognosis.

Microscopically, HC is composed of large polygonal eosinophilic hepatocyte-like neoplastic cells, arranged in trabecular and cords, with or without glandular formation.⁹⁻¹¹ PAS-positive and diastase resistant intracytoplasmic eosinophilic globules can be observed.⁹ As the cytomorphology is similar to HCC, a panel of immunohistochemistry markers should be carried out to ascertain the primary origin of the tumour. A literature review by Su *et al.* suggested a few important IHC markers which include AFP, Glypican-3, Hep Par-1 and CK19.⁴ When compared to HCC, HC were positive for AFP in 92% of cases, with positivity for Glypican-3 and CK19 (both 100%) and Hep Par-1 (38%).⁴ Hep Par-1 is a marker for both normal and neoplastic hepatocytes. A prior study reported Hep Par-1 sensitivity of 92.3% and specificity of 96.6% for hepatocellular carcinoma when compared to other non-hepatic tumours.¹⁷ A negative Hep Par-1 strongly suggests an extrahepatic origin.⁴ Normal and neoplastic hepatocytes are generally negative for CK7, CK19 and CK20.¹² Our tumour showed strong positivity for CK19 with negative CK7 and CK20, which correlates with the HC profile. In addition, HC are also frequently positive for CK18 (100%), pancytokeratin AE1/AE3 (92.3%) and alpha 1-antitrypsin (91.2%).⁴ Another promising marker, palate, lung and nasal epithelium carcinoma-associated protein (PLUNC), may also help in distinguishing HC from HCC, as it is detected in liver metastases of HC, but not in HCC.¹⁴

It is noteworthy to mention the elevation of serum AFP level is a unique feature of HC and is seen in more than 85% of cases. The AFP

is produced by the tumour itself, thus they are known as AFP-producing tumour.⁴ However, this serum AFP elevation is not essential for diagnosis of HC, as the emphasis is on the histological resemblance to HCC, irrespective of the AFP production.¹¹ Other possible lesions associated with elevated serum AFP needs to be ruled out, such as hepatoblastoma and germ cell tumour (especially yolk sac tumour). Similarly, the increase in serum AFP level does not necessarily associated with a positive AFP immunohistochemical staining. This is illustrated in a study of 634 cases of gastric carcinoma by Wang *et al.*, which showed that out of 45 cases that have elevated serum AFP, only 29 cases presented with positive immunohistochemistry staining in the tumour tissue.¹³

CONCLUSION

It is histologically challenging to differentiate between HC and HCC as they can mimic each other in terms of clinical presentation, radiology findings as well as tumour morphology. This is especially true when both liver and oesophageal masses are present simultaneously. Clinical and radiological correlation, coupled with tumour histology and a panel of immunohistochemistry staining will aid in diagnosis in difficult cases. As there is no specific immunohistochemical marker that can completely differentiate HC from HCC, a panel of stains such as CK19, Glypican-3, AFP and CK19 is highly recommended, with detailed clinical history, radiology and endoscopic findings to help achieve accurate diagnosis.

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