Focal Hepatocellular Carcinoma in Pancreas

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Abstract

A 67-year-old man was found to have a pancreatic head mass on abdominal ultrasound. He had compensated liver cirrhosis due to hepatitis C. The fine-needle aspiration (FNA) biopsy of the mass reported an adenocarcinoma of the pancreas, while the subsequent histopathology report of the supraclavicular lymph node showed features of hepatocellular carcinoma (HCC). A second read and additional stains on the FNA specimen confirmed a hepatoid (hepatocellular) carcinoma of the pancreas. He received atezolizumab and bevacizumab and had a good response. Tumors with features of HCC outside of the liver rarely occur and even more rarely in pancreas, with less than 50 cases reported so far. Pure HCC-like morphology is the most common histological form among four subtypes and has a relatively better prognosis. Surgical resection is considered the treatment of choice if amenable and variable outcomes are reported with different chemotherapies. Challenges exist in the diagnosis and the management of this rare and intriguing entity, and the potential misdiagnosis can have grave consequences as the management is completely different for a pancreatic adenocarcinoma and hepatoid carcinoma. We report a case with a challenging diagnosis of metastatic pancreatic hepatoid carcinoma which was treated as unresectable HCC with immunotherapy and the patient had a good response.

Keywords: Hepatoid carcinoma; Pancreatic hepatoid carcinoma; Hepatocellular carcinoma; Pancreatic carcinoma

Introduction

Hepatoid carcinoma (HC) is a rare tumor with features morphologically and immunohistochemically like focal hepatocellular carcinoma (HCC) [1]. It was first described in the stomach in 1985 [2] and pancreatic hepatoid carcinoma (PHC) was described in 1999 [3]. Primary sites such as the stomach, esophagus, lungs, gall bladder, urinary bladder, colon, ampulla of Vater, uterus, fallopian tubes, adrenal glands, ovaries, thymus, biliary tract, and other sites have been reported with HC [4, 5], with stomach being the most common location [5]. It is a very rare occurrence in the pancreas.

To the best of our knowledge, less than 50 cases of PHC have been reported so far in the literature. A review of literature shows that the diagnosis of PHC is mainly achieved through morphological analysis and immunohistochemical staining of the tissue specimens, since the clinical manifestations and laboratory tests are non-specific and it does not have unique radiological characteristics to set it apart from other pathologies [4]. Even the special staining required for its diagnosis might not be available at every institution. All these factors make the diagnosis difficult. It is even more challenging in cases with metastasis to the liver because a primary cancer of the liver is the closest differential. We report our experience of HC in pancreas which will add valuable information to the current literature on the diagnosis and treatment as well outcome of this rare entity.

Case Report

Investigations

A 67-year-old male with compensated cirrhosis due to hepatitis C, diabetes mellitus type II, hypertension, hypothyroidism, hyperlipidemia, and gastroesophageal reflux disease (GERD) presented with poor appetite and weight loss, progressively worsening over 3 months. He was lost to follow-up prior to that for approximately 2 years.

Diagnosis

A liver ultrasound (US) was done and showed a 70 mm pancreatic head mass, liver cirrhosis and gallbladder sludge. To further delineate the mass, a computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast was done and showed a 101 mm pancreatic head mass consistent with a neoplastic disease, intra- and extrahepatic biliary dilatation was seen and there was a 41.8 mm mixed attenuation mass in lateral right hepatic lobe, suggesting metastatic neoplastic
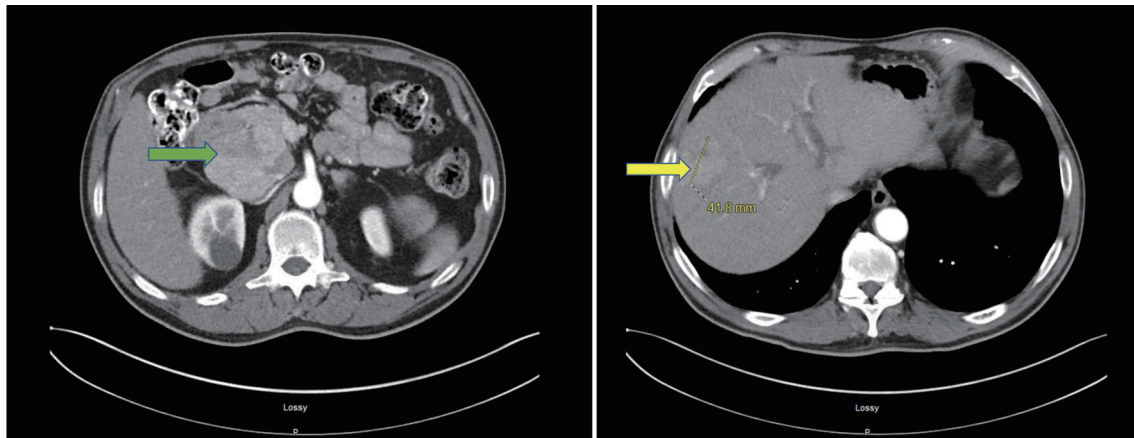
Figure 1. CT of abdomen and pelvis with IV contrast. A 101 × 69 mm mixed attenuation mass involving the head of pancreas (green arrow) is shown. Pancreatic duct dilation is not seen. Fatty infiltration of the liver with 41.8 × 63 mm mixed attenuation mass in the right hepatic lobe (yellow arrow) is shown. A right renal parenchymal cyst is seen. CT: computed tomography.

disease (Fig. 1). CA 19-9 levels were 24 U/mL (normal: < 35 U/mL). Alfa-fetoprotein (AFP) levels were markedly elevated at 411 ng/mL (normal: < 8.4 ng/mL). An endoscopic US with fine-needle aspiration (FNA) of the mass was done with a pre-procedure diagnosis of solid pancreatic neoplasm (likely adenocarcinoma) with metastasis. Color Doppler imaging was done prior to needle puncture to confirm lack of vascular structure in the path of the needle. Four passes were made with a 22-gauge needle using a trans-duodenal approach and a stylet was used. The US showed a common biliary duct (CBD) dilated at 7 mm and pancreatic duct at 2 mm. There was an oval mass in the head of pancreas which measured 100 × 80 mm in diameter (Fig. 2). Sonographic evidence also suggested invasion into portal vein. The FNA specimen was initially reported as exocrine pancreatic adenocarcinoma. Oncology team was taken on board. Fluorodeoxyglucose positron emission tomography (PET) scan was done to delineate metastatic disease, which showed a 32.3 mm hypermetabolic left clavicular mass, suggesting confluent lymphadenopathy, cirrhotic liver and hepatic metastatic neoplastic disease was not definitely visualized. There was moderate intrahepatic/extrahepatic biliary dilation. A 79.7 mm hypermetabolic mass

was again visualized in the head of the pancreas. An excisional supraclavicular lymph node biopsy was performed and it had features consistent with metastatic hepatoid (hepatocellular) carcinoma.

The patient developed signs and symptoms of obstructive jaundice including pale colored stools and dark urine. Laboratory workup was significant for elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at 207 and 349 U/L, respectively (normal: 10 - 50 and 7 - 52 U/L), elevated alkaline phosphatase 298 U/L (normal: 34 - 104 U/L), and increased total bilirubin 5.9 mg/dL (normal: 0.3 - 1.0 mg/dL) with direct bilirubin levels at 4.5 mg/dL (normal: 0.0 - 0.4 mg/dL). Patient was scheduled for a magnetic resonance imaging (MRI) of the abdomen and pelvis and a plan for a liver biopsy after that. MRI showed moderate central biliary ductal dilation secondary to mass effect from the pancreatic head mass, T1 hypointense lesions predominantly in the right hepatic lobe, consistent with metastasis and intra-and extrahepatic duct dilations. Pancreatic head mass measured at 61 × 77 × 117 mm, obstructing distal CBD, and encasing the common hepatic artery and abutting the portal vein. The appearance of the pancreatic head mass

Figure 2. An oval mass measuring 100 × 80 mm in the head of pancreas seen on endoscopic ultrasound (blue arrow).
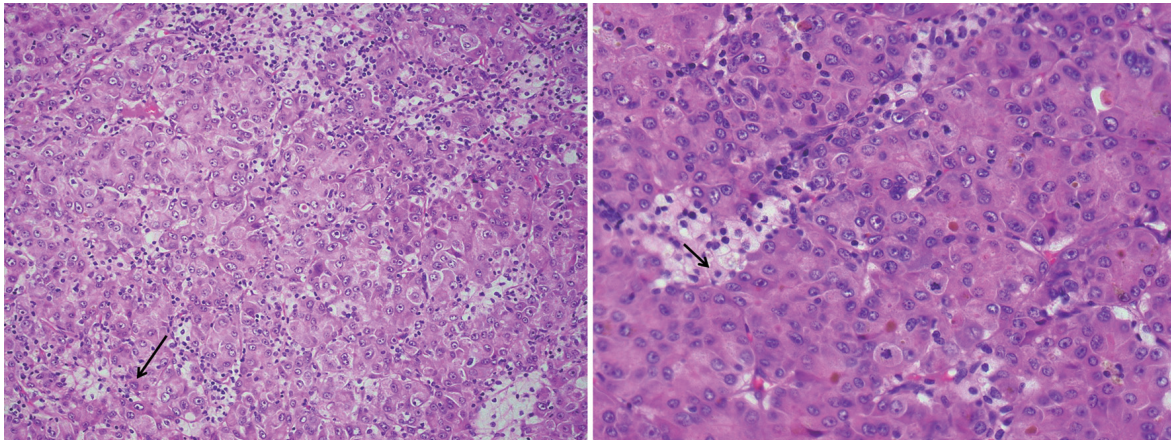
Figure 3. Hematoxylin and eosin stain of lymph node specimen showing small and large nests of neoplastic cells with large amount of cytoplasm, prominent nucleoli and intranuclear inclusions (thin black arrows). Few areas of tumor necrosis are seen.

was thought to be atypical for primary pancreatic cancer. Unfortunately, a liver biopsy was not done as the patient was admitted to the hospital. He underwent an endoscopic retrograde cholangiopancreatography (ERCP) procedure showing the main bile duct contained a single segmental stenosis of 20 mm in length, the common hepatic duct and left and right hepatic ducts, and all intrahepatic branches were severely dilated, secondary to a stricture likely from malignancy. A temporary plastic stent was successfully placed. The patient's symptoms improved significantly after the procedure; hence he was discharged home.

A consideration was given to initial diagnosis of adenocarcinoma of the pancreas in light of all the clinical and radiological information, and excisional lymph node histopathology. Additional immunohistochemical staining and evaluation of the pancreatic FNA sample confirmed a hepatoid (hepatocellular) carcinoma of the pancreas. The neoplastic cells were strongly positive for Cam 5.2, Hep Par-1, arginase-1, glypican-3, villin, beta-catenin and SMAD-4 (Figs. 3-5). This also correlated with the morphologic and immunostaining pattern of malignant cells in the lymph node. Because of the clinical and radiological presentation and histomorphology features, the metastatic deposit in the lymph node was deemed to be of pancreatic origin, likely a PHC. The smaller tumors in the liver were likely metastatic deposits from the PHC and less likely a separate neoplastic disease.
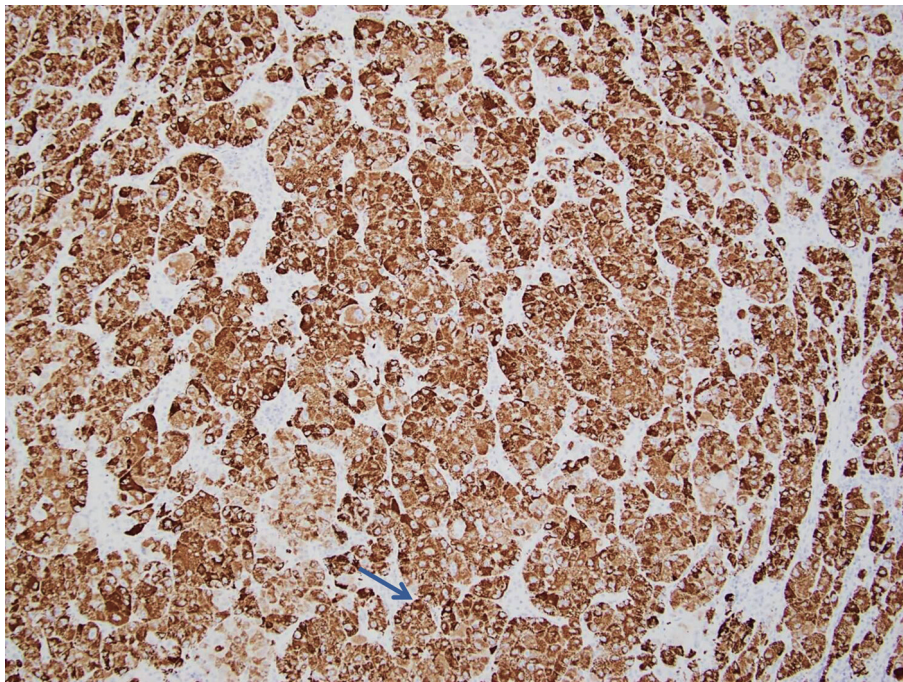

Figure 4. Pancreatic FNA specimen showing tumor cells staining positive for Hep Par-1 on immunohistochemical stain (thin blue arrow). FNA: fine-needle aspiration.
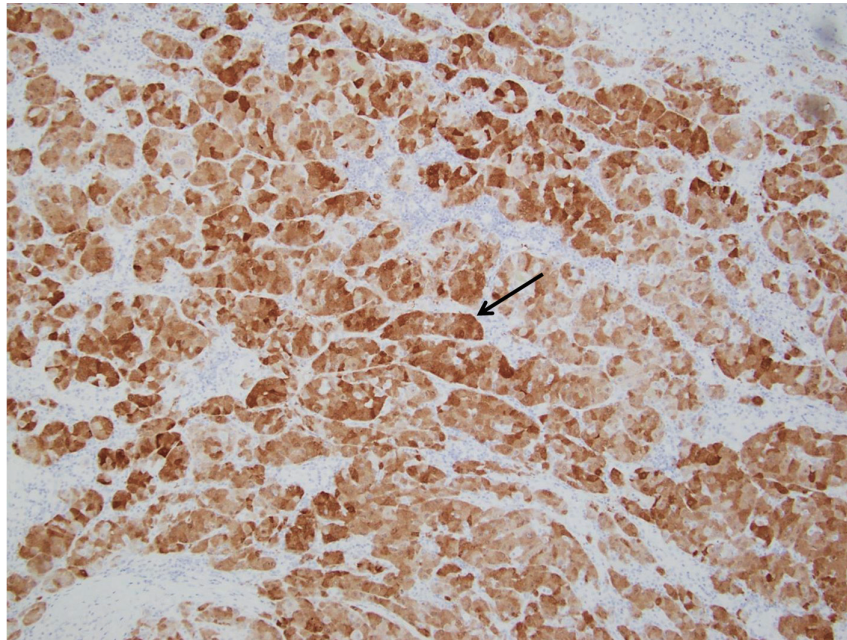
Figure 5. Pancreatic FNA specimen showing tumor cells staining positive for arignase-1 on immunohistochemical stain (thin black arrow). FNA: fine-needle aspiration.

Treatment

The patient was started on atezolizumab and bevacizumab therapy, and regularly followed up with the oncologist to monitor response to therapy.

Follow-up and outcomes

Imaging studies including PET scans showed stable disease (or even minimal improvement) for up to 14 months of continued treatment with atezolizumab and bevacizumab and the patient tolerated the therapy relatively well. The patient's disease progressed, based on the increased AFP levels, i.e., approaching 1,000 U/mL (normal: < 35 U/mL), and the increase in the size of liver lesions on CT scan of the abdomen and pelvis. Therapy with atezolizumab and bevacizumab was stopped and he was started on lenvatinib. He developed infection with COVID-19 followed by an episode of sinusitis 2 weeks later. Lenvatinib was ultimately discontinued (about 2 months later) due to symptoms like worsening shortness of breath and abdominal pain, and weakness in the setting of recent COVID-19 infection, being on targeted chemotherapy with lenvatinib and increased overall burden of the disease. Therapy with tremelimumab and durvalumab was initiated but the patient was hospitalized for a fever of unknown origin a week later. The patient was discharged to hospice care and passed away two and a half weeks later.

Discussion

The patient's presentation in combination with imaging and initial pancreatic biopsy report, all pointed towards a metastatic adenocarcinoma of the pancreas. The supraclavicular biopsy specimen had features of a hepatoid (hepatocellular) carcinoma. Additional staining of the pancreatic FNA specimen along with an abdominal MRI findings of multiple liver lesions suggested a diagnosis of PHC with metastasis to liver and left supraclavicular lymph node.

The theories proposed to explain pathogenesis of PHC are: 1) pancreas has ectopic liver tissue where an HC originates [6-8]; 2) the pancreatic cells transdifferentiate into hepatocytes [8, 9]; and 3) liver and pancreas are both derived from the foregut endoderm and there may be activation of the genes controlling hepatic differentiation of pancreatic cells during carcinogenesis, which are normally suppressed [3, 10]. The most common location for PHC is pancreatic tail [1].

In a recent literature review of 41 cases, four histological subtypes were noticed: pure HCC-like morphology, with neuroendocrine differentiation, and with acinar or glandular differentiation [4]. Different terms have been used for the subtype with pure HCC such as hepatoid carcinoma, hepatic adenocarcinoma, hepatoid variant of pancreatic cancer, primary HCC of the pancreas, a pancreatic tumor with hepatoid differentiation or ectopic HCC, etc. [11].

HC has a histological appearance of proliferating large tumor cells, with a trabecular pattern of large polygonal cells seen with abundant eosinophilic cytoplasm, central nuclei, and nucleoli [12]. A majority of PHC cases have elevated serum AFP levels, hence it can be used as a marker to determine the success of surgery or response to chemotherapy [4]. Certain primary pancreatic cancers can have elevation in AFP levels, including ductal carcinoma, neuroendocrine, germ cell tumors and undifferentiated pancreatic adenocarcinoma [13, 14]. AFP, Hep Par-1, glypican-3, arginase-1, anti-albumin,

anti-α-1-antitrypisine, anti-low molecular weight cytokeratin, anti-epithelial membrane antigen antibodies and CD10 are the common immunohistochemical characteristics between PHC and HCC. Focal canalicular patterns in PHC on poly-clonal carcinoembryonic antigen (CEA) stains have also been reported [15-17]. Hep Par-1 is thought to be the most sensitive among these markers [18]. Metastatic HCC from the liver and HC from another site are the closest differentials [4]. Two specific hepatocyte transporters i.e., bile salt export pump (BSEP) and multidrug resistant protein 3 (MDR3) which are only expressed by HC cells, have been suggested to differentiate [14], but they are not available everywhere. Acinar cell carcinoma is similar to HC and often shows positivity for AFP and Hep Par-1 markers on immunohistochemical staining. Seventy-five percent of HCs are positive for arginase-1 while acinar cell carcinoma is always negative for it, hence arginase-1 can be used to distinguish between the two [19].

There is no consensus on treatment protocol due to limited number of cases reported in the literature. Surgical resection is considered the preferred option [4, 12]. Oral multitar-get tyrosine kinase inhibitor, sorafenib, resulted in a 7-month progression-free survival, in a case of metastatic PHC [20]. A 13-month progression-free survival was reported in a case of PHC with liver metastasis treated with neoadjuvant modified-FOLFIRINOX (MFOLFIRINOX) chemotherapy followed by surgical resection [21]. A 46-month survival was reported in a patient with pancreatic neuroendocrine carcinoma treated with six cycles of chemotherapy (gemcitabine intravenously) after successful surgery [22]. Next-generation nucleic acid sequencing can be used for detection of mutated genes, hence helping define the characteristics of the tumor as well as the choice of chemotherapy. It is a novel approach for rare tumors that was used in a few instances of PHC with promising results [23, 24]. We chose a combination therapy of atezolizumab and bevacizumab as this combination showed better overall and progression-free survival outcomes compared with sorafenib in patients with unresectable HCC, in the IMbrave150 trial. The hazard ratio for death with atezolizumab-bevacizumab compared to sorafenib was 0.58 (95% confidence interval (CI): 0.42 - 0.79; $P < 0.001$), and overall survival at 12 months was 67.2% (95% CI: 61.3 - 73.1) versus 54.6% (95% CI: 45.2 - 64.0) [25]. Tremelimumab plus durvalumab (STRIDE) combination therapy was noticed to significantly improve overall survival when compared to sorafenib in unresectable HCC, in the HIMALAYA trial [26]. Studies comparing STRIDE and atezolizumab plus bevacizumab head-to-head have not been conducted yet.

Prognosis is difficult to predict due to limited number of cases in the literature. PHC is thought to have an aggressive course. Among different subtypes of PHC, pure HCC-like morphology has a better outcome than other subtypes [4]. The 1-year and 5-year survival rates in a case series of 23 cases of HC were reported to be 71.1% and 40.4%, respectively. The median was 13 months, and the mean was 18.1 ± 21.8 months [11].

The present case had an interesting journey until the final diagnosis was made. Diagnosing rare pathologies is difficult in general, and it can be even more challenging when the entity has non-specific manifestations and lacks clearly defined diagnostic criteria. Furthermore, making the correct diagnosis is crucial in cases like metastatic PHC, as a misdiagnosis or a delay in the diagnosis can have grave consequences.

Learning points

PHC is a very rare tumor with limited number of cases reported in literature. Its diagnosis is challenging since it does not have characteristic clinical or radiological features and elevated AFP might be a clue. The diagnosis is invariably through special staining of the tissue specimen. Long-term survival is better in patients where the tumor is resected compared to chemo-/immunotherapy. Metastasis to other organs such as liver and lymph nodes is a poor prognostic indicator.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from the patient.

Author Contributions

Yasir Ahmed: wrote/drafted the manuscript, and final review and editing. Usama Sakhawat: case description for initial draft, review process. Fahad Malik: review of literature, editing. Saadia Haleema: description of histopathology slides. Daniel Chin: review of literature, editing. Ali Marhaba: supervisor, conceptualization, final review and editing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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