Approach to the Diagnosis of Hepatoid Adenocarcinoma, an Under-reported Entity: Case Series and Review of Literature

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Abstract
Hepatoid adenocarcinoma is a rare type of extra-hepatic adenocarcinoma which exhibits morphological, functional, and immunohistochemical features of hepatocellular carcinoma, hence correct diagnosis poses a challenge. The most frequent site of this tumor is stomach and rarely occurs in ovaries, lung, gallbladder, pancreas, uterus, and other sites. We present four cases of hepatoid adenocarcinoma of our hospital at rare sites like lungs and gallbladder along with literature review and a simplified approach to diagnosis. In absence of adequate immunohistochemistry or radiological findings often this entity is missed or misdiagnosed as metastatic hepatocellular carcinoma. We have analyzed these hepatoid adenocarcinoma cases in terms of various clinical, serological, histo-morphological, and immunohistochemical parameters, and propose a systematic approach to correctly diagnose this entity.

Keywords
► hepatoid adenocarcinoma  
► hepatocellular carcinoma  
► hepatoid differentiation  
► AFP  
► liver

Introduction
Hepatoid adenocarcinoma (HAC) is a tumor with aberrant hepatocellular differentiation that occurs in extrahepatic organs. HAC was first recognized as a gastric tumor in 1985 by Ishikura et al.,1 as defined by having an extremely high serum level of AFP and morphological features similar to hepatocellular carcinoma (HCC).2 The most common site of HAC is gastric (63%), followed by ovaries (10%), lung (5%), gallbladder (4%), pancreas (4%), and uterus (4%).3 Since its description by Ishikura, there have been only case reports and few review articles regarding this rare but important entity. Finding the primary tumor origin of HAC is crucial, and prompt and adequate treatment may improve outcomes of patients. However, HCC with various extrahepatic metastases such as to the stomach has been reported, and determining the tumor origin may become a challenge for physicians, especially when clinicopathological findings of liver tumors are not typical for HCC.4

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Case 1

A 52-year-old male presented with chief complaints of chest pain and on–off fever since 8 months. CT scan revealed soft tissue mass lesion in left upper lobe of lung measuring 6.1 × 5.2 cm along with few pleural, fissural, and parenchymal nodules in both the lung parenchyma. A sub centimeter-sized hypodense lesion in segment IVB of liver was noted with a few enlarged necrotic nodes seen in gastro-hepatic, cardio-phrenic, and paraaortic region. Serum carcinoembryonic antigen (CEA) levels were raised whereas serum α-fetoprotein (AFP) levels and Ca 19.9 levels were within normal range (Table 1).

Lung biopsy was performed from left upper lobe lesion and microscopy revealed presence of tumor in the form of glands, nests, and islands of tumor cells having vesicular nuclei, eosinophilic cytoplasm and prominent eosinophilic nucleoli suggesting a diagnosis of adenocarcinoma with hepatoid features. Immunohistochemistry was done which showed tumor cells positive for CK7, CK20, MOC-31, and Heppar-1; while calretinin, TTF-1, synaptophysin, and chromogranin were negative (Table 2).

Case 2

A 72-year-old female presented with chief complaints of loss of appetite and on–off fever since 3 months. CT thorax revealed right upper lobe lung mass measuring 7 × 8 cm along with multiple metastatic lesions in both the lung lobes, liver, mediastinal, and right supraclavicular lymph nodes (Fig. 1). Serum LDH level was raised whereas serum AFP, Ca19.9, and CEA levels were within normal limits (Table 1).

Right supraclavicular lymph node biopsy was done which revealed microscopically presence of metastatic poorly differentiated carcinoma with hepatoid features. Immunohistochemistry was done (Table 2) and tumor cells were found positive for CK7, Heppar1, MOC-31, and AE1/AE3, whereas

<table>
<thead>
<tr>
<th>Case</th>
<th>AFP</th>
<th>CA19.9</th>
<th>CEA</th>
<th>LDH</th>
<th>CA125</th>
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<tr>
<td>Case 1</td>
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<td>Raised</td>
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</tr>
<tr>
<td>Case 3</td>
<td>Normal</td>
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<td>Case 4</td>
<td>Normal</td>
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<td>Not done</td>
<td>Raised</td>
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</table>

<table>
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<tr>
<th>CK7</th>
<th>CK20</th>
<th>Heppar 1</th>
<th>MOC 31</th>
<th>Glypican-3</th>
<th>TTF1</th>
<th>WT1</th>
<th>P63</th>
<th>S100</th>
<th>PS3</th>
<th>Synaptophysin</th>
<th>Chromogranin</th>
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<tr>
<td>CASE 1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Not done</td>
<td>–ve</td>
<td>–ve</td>
<td>+</td>
<td>–ve</td>
<td>Weak</td>
<td>–ve</td>
<td>–ve</td>
</tr>
<tr>
<td>CASE 4</td>
<td>Weak</td>
<td>+</td>
<td>–ve</td>
<td>–ve</td>
<td>+</td>
<td>+</td>
<td>–ve</td>
<td>Not done</td>
<td>Not done</td>
<td>–ve</td>
<td>Not done</td>
</tr>
</tbody>
</table>

Fig. 1 (A) Axial contrast enhanced CT image of the chest in mediastinal window setting showing an enhancing lung mass lesion (blue arrow). (B) Corresponding tumor on histopathology with surrounding lung parenchyma (H&E, 40x).
they were negative for CK20, calretinin, synaptophysin, and chromogranin. Hence, the diagnosis of HAC was made with the help of immunohistochemistry.

**Case 3**

A 55-year-old female presented with non-specific complaints of pain in abdomen and dyspepsia since 20 to 25 days. CT abdomen revealed mass in the body and fundus of gallbladder measuring 3 × 2.1 cm with infiltration of adjoining segment IV of liver and metastatic periportal lymph nodes. Suspicious metastatic adenoidal nodule with retroperitoneal lymph nodes were also present. CA-125 levels were slightly raised with normal levels of AFP, Ca19.9, and CEA (→Table 1).

Periportal lymph node biopsy was performed and microscopy revealed metastatic adenocarcinoma with hepatoid features. The tumor was arranged in the form of glands and nests of polygonal tumor cells with vesicular chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm. On immunohistochemistry, (→Table 2) tumor cells were positive for CK7, MOC-31, Hep-par1, and negative for CK20, TTF-1, synaptophysin, and chromogranin.

**Case 4**

A 46-year-old female presented with non-specific pain in abdomen. CT scan revealed mass in left lobe liver along with suspicious nodules in the lung. Serum CEAs were mildly raised whereas serum (→Table 1) AFP levels and Ca 19.9 levels were within normal range. Patient underwent left lobe of liver wedge resection and was reported with possibilities of high grade carcinoma and adenocarcinoma with hepatoid morphology.

Later on right lower lobe lung resection was done which on microscopy showed nests of tumor cells separated by thick fibrovascular stroma. Cells were polygonal in shape, having round to oval hyperchromatic nuclei and prominent nucleoli suggesting a diagnosis of HAC. Immunohistochemically, tumor cells were positive for MOC-31, Glypican-3, weakly positive for CK7 and negative for CK20, TTF-1, synaptophysin, and chromogranin (→Table 2).

**Discussion**

HAC is a rare type of extrahepatic adenocarcinoma which exhibits morphological, functional, and immunohistochemical features of HCC.

It usually occurs in elderly age group. Lee et al presented a case of HAC in gallbladder in 61-year-old male, similar to Qian et al who also reported gallbladder HAC in 61-year-old male. Ellouze et al also reported gallbladder HAC in a 59-year-old female. Grossman et al presented a case of HAC lung in a 54-year-old male. In our cases, the mean age was 56.25 years ranging from minimum 46-year-old female to maximum 72-year-old male.

According to literature review, most common site is stomach followed by ovary, lung, gallbladder, pancreas, uterus and other extremely rare sites like esophagus, peritoneum, rectum, transverse colon, testis, ovary, jejunum, ureter which are only reported as single case reports. Albeit stomach being the most common site, we encountered three cases of HAC in lungs and one in gallbladder.

Typically, an elevated level of serum AFP is associated with HAC, although normal levels have also been reported. HAC does not always produce AFP. Emphasizing the fact that although AFP positivity is important, it is not essential for a diagnosis of HAC. According to Su et al, most HAC patients examined had elevated serum AFP (84.8%); whereas all the four cases reported at our hospital presented with normal levels of AFP.

Very few case reports of HAC are present in the Indian literature and are summarized in →Table 3. Nargund et al and Vellaisamy et al presented the cases of HAC in lung and Devi presented the case with site of tumor in gallbladder. In most of the case reports, AFP levels were increased; however, similar to our cases, Devi et al presented the case with normal levels of AFP. On immunohistochemistry, CK7 was positive and CK20 was negative in the studies done by Vellaisamy et al and Nargund et al, whereas CK7 was negative in the case reported by Devi et al, in which they demonstrated positivity of CK19. Veerankutty et al also reported CK7 negative in their case, whereas positive for CK8 and CK18. In most of the studies, Hep-par 1 or AFP immunostaining was done for confirming hepatoid differentiation, however, in the present study in addition to Hep-par 1, MOC-31 immunostaining was also done for confirmation of adenocarcinoma component.

HAC was named after its characteristic histopathological features, showing hepatoid differentiation resembling HCC. Histomorphologically, the tumor is composed of hepatoid cells arranged in sheets and trabecular pattern. These neoplastic cells are polygonal with eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. Medullary proliferation, papillary, tubular, and rosette patterns have also been reported in literature. Therefore, the main differential diagnosis of HAC in gallbladder and lung is metastatic HCC. Clinically, HAC tumors are large bulky masses in lungs but may present as smaller nodules similar to metastatic HCC. HCC is usually associated with higher levels of AFP but so is HAC in most of the cases, although few cases may show normal levels of AFP, as seen in present study.

We propose a stepwise approach for diagnosis of HAC which can be helpful for confident reporting of this under diagnosed entity (→Fig. 4). If the morphology of hepatoid differentiation at any extrahepatic site along with raised or normal AFP levels is noted, this should raise the possibility of HAC. Further in this step, IHC can be quite helpful to rule out HCC and adenocarcinoma differentials: CK7 positivity, MOC-31 positivity for adenocarcinoma differentiation, and Hep-par1/Glypican-3 positivity for hepatoid differentiation. If MOC-31, CK7, and Hep-par1/glypican-3 all are positive; whereas CK20 is negative, this IHC panel result supports the diagnosis of HAC. If only Hep-par1/glypican-3 is positive but MOC-31, CK7 and CK20 are negative, this favors the diagnosis of HCC. When MOC31 is positive and either CK7
or CK20 or both are positive but Heppar-1 and glypican 3 are negative, this supports the diagnosis of adenocarcinoma.

HACs are considered as very aggressive tumors with poor prognosis. The prognosis of lung HAC and HCC metastatic to the lungs is usually poor but, when HAC presents as localized disease, resection for long-term cure is possible.\(^2\) Patients suffering from HAC of the gallbladder have a poor prognosis; therefore, correctly identifying the hepatoid component within gallbladder cancer and providing suitable treatment for patients is crucial.\(^4\) As said earlier, histomorphological features are the most important for identification of this underreported entity but an amalgamation of radiological,

### Table 3 Indian review of literature (PubMed Source)

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>First author</th>
<th>Year</th>
<th>No. of cases Of HAC reported</th>
<th>Age and sex</th>
<th>Location of tumor</th>
<th>AFP levels</th>
<th>IHC markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Arijit Majumdar(^13)</td>
<td>2013</td>
<td>1</td>
<td>55-y female</td>
<td>Stomach</td>
<td>Increased</td>
<td>Positive-AFP</td>
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<td>2</td>
<td>Vidisha Mahajan(^14)</td>
<td>2014</td>
<td>1</td>
<td>60-y male</td>
<td>Stomach</td>
<td>Increased</td>
<td>Positive-AFP, CK8, 18, focal CEA. Negative-Heppar-1.</td>
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<td>3</td>
<td>Fadl H. Veerankutty(^12)</td>
<td>2015</td>
<td>1</td>
<td>47-y male</td>
<td>Pancreas</td>
<td>–</td>
<td>Positive-HSA, glypican-3, AE1/AE3, CK8, CK18, weakly AFP. Negative-Ck7, EMA, Chromogranin.</td>
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<tr>
<td>4</td>
<td>Nalli R. Sumitra Devi(^11)</td>
<td>2015</td>
<td>1</td>
<td>43-y male</td>
<td>Gall bladder</td>
<td>Increased</td>
<td>Positive-Ck19, CEA, Heppar-1, focal AFP. Negative-Ck7, Ck20.</td>
</tr>
<tr>
<td>6</td>
<td>Siva Gavin(^15)</td>
<td>2020</td>
<td>1</td>
<td>53-y female</td>
<td>Stomach</td>
<td>–</td>
<td>Positive-AFP, α1antitrypsin, α1chymotrypsin</td>
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<td>8</td>
<td>Present study</td>
<td>2021</td>
<td>4</td>
<td>52-y male, 72-y female, 55-y female, 46-y female</td>
<td>Lung and gall bladder</td>
<td>Normal in all cases</td>
<td>Positive-AE1/AE3, MOC31, CK7, Heppar-1/Glypican-3. Negative-TTF-1, S-100synaptophysin, chromogranin and S-100. (► Figs. 2 and 3).</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen.

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**Fig. 2** (A) Tumor cells exhibiting moderate nuclear pleomorphism, prominent nucleoli, and eosinophilic cytoplasm (H&E, 200X). (B, C, D) Tumor cells showing positive immunostaining for AE1/AE3, Heppar-1, and MOC-31.

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**Fig. 3** (A, B) Tumor cells showing positive immunostaining for CK7 and negative for CK20. (C) Histiocytes are highlighted by S-100 immunostain, while tumor cells are negative. (D) TTF-1 immunostaining highlights the lung parenchyma, while tumor cells are negative.
histopathological, biochemical, and immunohistochemistry findings can help to reach the specific diagnosis of HAC.

Conflict of Interest
None declared.

References

