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## Hepatoid adenocarcinoma of the stomach – A rare clinicopathological entity

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### Abstract

**Background:** Hepatoid adenocarcinoma of the stomach is a rare form of gastric carcinoma with specific clinicopathological features and extremely poor prognosis.

**Materials and methods:** Here, we discuss 3 cases who presented in the outpatient department with pain abdomen and constitutional symptoms. Radiological examination revealed a growth involving the antrum of the stomach while the liver and spleen were normal. One case with the endoscopic biopsy suggestive of neuroendocrine tumour underwent sleeve gastrectomy and two other with biopsy suggestive of grade 3 adenocarcinoma underwent distal radical gastrectomy.

**Results:** In all the three cases the tumor showed hepatoid features and was immunohistochemically positive for alpha fetoprotein. All the 3 received adjuvant chemotherapy and radiotherapy. One patient showed anastomotic recurrences in one year of follow up.

**Conclusions:** Though known to be an aggressive neoplasm early diagnosis of hepatoid adenocarcinoma can help improve the prognosis of the disease.

**Keywords:** Hepatoid adenocarcinoma, gastric cancer, AFP, HSA, poorly differentiated

### 1. Introduction

Hepatoid adenocarcinoma is a rare variant of adenocarcinoma of the stomach with a very poor prognosis. Hepatoid adenocarcinoma is characterized by a distinct morphology, immunohistochemistry and in many cases by increased serum alpha fetoprotein (AFP) levels. Microscopic findings include both adenocarcinomatous and hepatoid elements. The diagnosis of hepatoid adenocarcinoma of stomach is not dependent on whether alpha fetoprotein is produced; actually, histological features are important for diagnosis. The presenting symptoms are similar to those that of conventional adenocarcinomas. Hepatoid adenocarcinoma is an adenocarcinoma primarily originating from gastric mucosa and contains distinctive foci of hepatocellular differentiation. Periodic acid Schiff (PAS) positive diastase resistant hyaline globules in the tumor cells are a common but not a specific finding seen in the hepatoid adenocarcinomas<sup>[1]</sup>.

The incidence of this variant ranges from 0.38% to 0.73% of all gastric cancer<sup>[2]</sup>. To date, HAC has only been reported in case series or single case reports. Awareness of this rare entity would aid in better diagnosis by the pathologist and management by treating physicians.

We describe here 3 cases of this rare entity of hepatoid adenocarcinoma of the stomach, and review the literature concerning the clinicopathological aspects of the cases.

### 2. Materials and methods

We collected the data of 3 cases operated in our department in the last 2 years. All the 3 patients underwent evaluation with esophagogastroduodenoscopy (EGD) and biopsy and contrast enhanced CT scan of the abdomen along with other routine workup. The latest follow up data of the patients was collected. Two cases underwent distal radical gastrectomy (DRG) and D2 lymphadenectomy (D2LND) and one patient underwent sleeve gastrectomy.

### 3. Results

The clinicopathological features of the operated cases of hepatoid adenocarcinoma are depicted in the table. All the 3 patients presented with non-specific symptoms.

One patient with endoscopic biopsy not suggestive of adenocarcinoma but GIST (gastrointestinal stromal tumour)/NET (neuroendocrine tumour) underwent sleeve resection of stomach. All the patients received chemotherapy (CT) and radiotherapy (RT) postoperatively. One patient had local anastomotic site recurrence within 1 year of surgery.

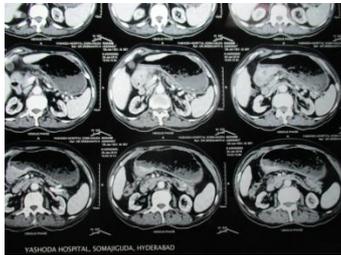


Fig. CECT abdomen of Case 3 showing mass in the antropyloric region



Fig. Endoscopic picture of antral growth of case 2

Table: clinicopathological features of 3 cases of hepatoid adenocarcinoma

|                 | Case 1                                                                                                                                                                   | Case 2                                                                         | Case 3                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------|
| Age / Sex       | 47/M                                                                                                                                                                     | 43/F                                                                           | 75/M                                                        |
| Complaints      | Vomiting, melena, constipation, LOW                                                                                                                                      | Epigastric pain, LOW, LOA- 3 months                                            | Dysphagia, nausea, vomiting, LOW, LOA since 1 month         |
| EGD             | Polypoidal growth in body along greater curvature                                                                                                                        | Antropyloric growth                                                            | Small hiatal hernia with antral growth                      |
| Biopsy          | 1 <sup>st</sup> chronic gastritis with mild dysplasia<br>2 <sup>nd</sup> ?NET<br>3 <sup>rd</sup> ?maltoma with chronic gastritis with ulceration                         | Grade 3 adenocarcinoma                                                         | Grade 3 adenocarcinoma                                      |
| CECT abdomen    | Heterogeneous enhancing soft tissue lesion from greater in the region of body with exophytic component with few sub-cm regional LN anterior to the body of stomach? GIST | Heterogeneous enhancing circumferential wall thickening of antropyloric region | enhancing mural thickening of antrum and pylorus of stomach |
| Date of surgery | 15.05.14                                                                                                                                                                 | 14.08.14                                                                       | 12.02.16                                                    |
| Surgery         | Sleeve gastrectomy+ omentectomy                                                                                                                                          | DRG+D2LND                                                                      | DRG+D2LND                                                   |
| Final HPE       | pT3N0, grade 3, margins free PNI/LVI -                                                                                                                                   | pT2N3aMx, LN-8/30 grade 3, PNI/LVI-, margins free                              | pT2N2Mx, LN 6/11, grade 3, margins free                     |
| IHC stains      | HSA/CK/NSE-positive, Cg A / Synaptophysin negative, Ki67 -10%,                                                                                                           | AFP+, HAS -                                                                    | HSA -, AFP +, her2neu +, CEA +, CgA -, CK 20 focal +        |
| Adjuvant CT     | 6 cycles                                                                                                                                                                 | 5FU+LVx 6                                                                      |                                                             |
| Adjuvant RT     | 50 G                                                                                                                                                                     | 45 G                                                                           |                                                             |
| Follow up       | Till 17.07.15 no recurrence                                                                                                                                              | Anastomotic recurrence in 12 months                                            | Lost for follow up                                          |

4. Discussion

Gastric hepatoid adenocarcinoma (GHAC) with elevated serum AFP, first described by Ishikura *et al.* 1985, [3] is a rare gastric cancer subtype seen more frequently in older patients, aged 60-70 years. The antrum is the most common site. There are no specific symptoms and signs, but generally, epigastric pain and fatigue are observed most frequently [4].

The term hepatoid has been restricted to those extrahepatic carcinomas that show histologic features of hepatocytic differentiation [1]. Foregut derivation of both liver and the stomach could be the likely reason for this increased incidence. Hepatoid adenocarcinoma has also been reported in several different organs including the esophagus, colon, lung, pancreas, peritoneum and ovary [4].

The diagnosis of hepatoid adenocarcinoma depends on recognition of characteristic histological features. The histological findings usually reveal intestinal adenocarcinoma with foci of hepatoid differentiation. Tumor cells in hepatoid foci histologically resemble the morphology of hepatocellular carcinoma (HCC). The

Immunohistochemical (IHC) staining pattern has been variably reported in the literature. The tumor shows positivity for alpha fetoprotein, polyclonal CEA, CK 8, CK 18 while negativity for CK7 and Hep Par-1 is seen [5]. The tumor in this case showed positivity for AFP in the hepatoid areas and focal positivity for polyclonal CEA. The adenocarcinomatous component may be well or poorly differentiated, often with clear cells and a papillary pattern [2]. The tumor can reveal a solid, trabecular and pseudoglandular arrangement mimicking the liver architecture. PAS positive hyaline globules within the tumor cells are another common but non-specific finding that has been correlated with production of AFP [6]. There is no consensus for the amount of hepatocellular differentiation required to classify a tumor as a hepatoid adenocarcinoma. GHAC, when present, need to be differentiated from HCC. Generally, in HCC, neighboring cirrhotic lesions can be seen and tumor cells are positive for Hep Par-1, a sensitive and specific immunohistochemical marker for hepatocyte differentiation, whereas in GHAC Hep Par-1 is often negative and neighboring cirrhotic lesions are seldom seen

[2]. P53 protein immunohistochemical detection in GHAC has also been demonstrated. In classic adenocarcinoma of the stomach, p53 protein is frequently expressed and often correlates with a poor prognosis. In contrast, overexpression of p53 is a rare event in HCC [7]. A recent finding indicates the use of the palate, lung, and nasal epithelium carcinoma-associated protein (PLUNC) immunostaining as a novel marker that distinguishes GHAC from primary HCC [8]. The absence of an underlying disease such as liver cirrhosis and the use of imaging modalities such as endoscopy and CT in our case ruled out the presence of the a primary hepatocellular carcinoma.

The presence of markers of hepatoid differentiation cannot be used as the sole diagnostic criteria for GHAC but must always be accompanied by a compatible morphological pattern [9]. Not all hepatoid adenocarcinomas produce AFP. Only 54% of the cases express AFP by immunohistochemistry and 63% reveal an elevated serum AFP levels [10]. Since the diagnosis of GHAC was made after surgery serum AFP levels were not done in our cases.

Hepatoid adenocarcinomas are reported to have aggressive behavior. Deep invasion of the gastric wall, frequent metastasis to regional lymph nodes and high incidence of liver metastasis have been observed. These tumors have a high proliferative activity, weak apoptosis and rich neovascularization indicating high grade malignant potential [11]. Two patients in our study had N2 and N3 nodal disease and all the three had high grade (III) tumors.

In terms of treatment, there are only sparse data in the literature pertaining specifically to GHAC, and the disease should be treated similarly to common gastric adenocarcinoma.

A specific treatment protocol for this variant has not yet been defined with the majority of patients being detected in the metastatic stage and requiring palliative chemotherapy. The overall 5 year survival rate of hepatoid adenocarcinoma was 9% when compared to 44% of conventional gastric carcinoma [12]. One patient had recurrence at anastomotic site within one year inspite of CT and RT. Early diagnosis of this histological variant is essential for curative resection of the disease.

## 5. Conclusions

The histologic pattern of hepatoid adenocarcinoma is unique and the incidence is rare. The literature describes the clinical course of hepatoid adenocarcinoma stomach to be worse than that of conventional adenocarcinoma. Thus distinction between these two entities is necessary, which can be accomplished histochemically and by measuring serum AFP levels. Early diagnosis of this histological variant is essential for curative resection of the disease. The rarity and poor prognosis of this clinicopathological entity requires greater awareness for diagnosis and management.

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