Case Report

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Pathology Section

Hepatoid Adenocarcinoma of the Stomach: A Case of Rare Tumour in an Unusual Subserosal Location

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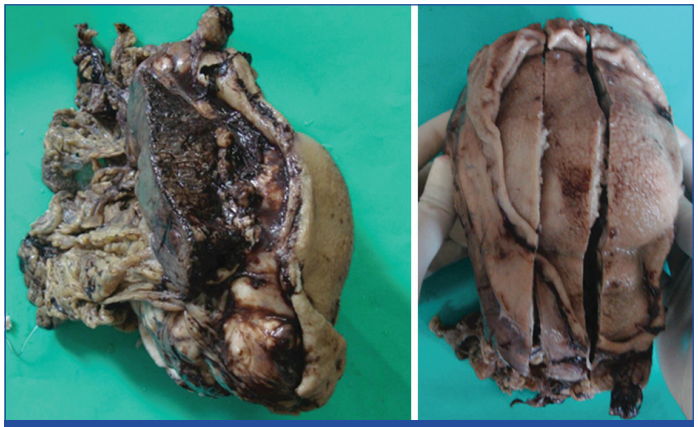
ABSTRACT

Hepatoid Adenocarcinoma (HAC) is a special type of adenocarcinoma of extrahepatic origin that has overlapping features with Hepatocellular Carcinoma (HCC). Herein, present case is of a 75-year-old man who presented with abdominal pain, bilious vomiting, and constipation for four days, along with a palpable mass in the abdomen for five months. Imaging studies revealed a mass in the subserosal region of the greater curvature of the stomach. Intraoperative findings showed a mass involving the stomach, liver, and omentum, initially suggesting a diagnosis of malignant Gastrointestinal Stromal Tumour (GIST). However, histopathological examination revealed lobules of polygonal cells with abundant eosinophilic to vacuolated cytoplasm and enlarged, moderately pleomorphic nuclei, indicating hepatoid differentiation. The aggressive nature of the lesion, invading the liver and omentum, the absence of risk factors for HCC, negative staining for CD 117 and polyclonal Carcinoembryonic Antigen (pCEA), and positive staining for glypican 3 and CK 19 on immunohistochemistry, confirmed the diagnosis of HAC of the stomach rather than HCC. After surgery, the patient was referred to an Oncology centre. An accurate diagnosis of HAC is crucial due to its aggressive nature and poor prognosis.

Keywords: Carcinoma, Glypican 3, Hepatocellular, Stomach neoplasms

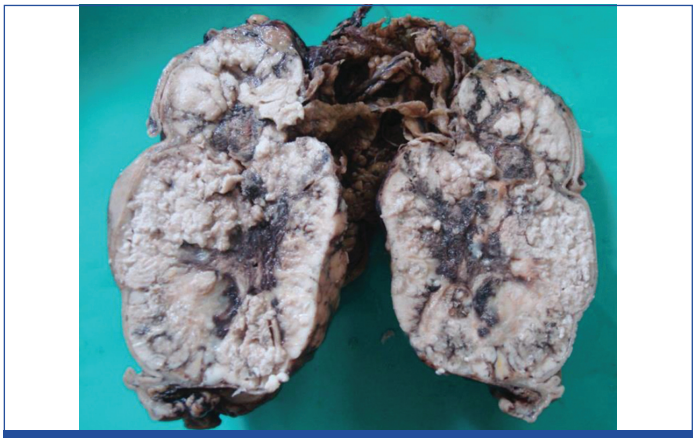
CASE REPORT

A 75-year-old male patient presented to the surgical OPD with complaints of severe abdominal pain, bilious vomiting, and constipation for the past four days. A past history of decreased food intake, weight loss, and a palpable abdominal mass for the past five months was noted. On examination, a diffuse hard mass was palpable in the upper third of the abdomen, involving the epigastrium and left hypochondrium. No lymphadenopathy was observed. Ultrasonography and Computed Tomography (CT) scan revealed a gastric mural growth along the greater curvature of the stomach. Based on these findings, the surgeon favoured a diagnosis of GIST. During the surgery, it was found that the tumour had infiltrated the left lobe of the liver and the omentum. Therefore, a partial gastrectomy, along with partial hepatectomy and omentectomy, was performed [Table/Fig-1-3]. The invasive nature of the tumour, indicated by its infiltration into the liver and omentum, led to a diagnosis of malignant GIST.

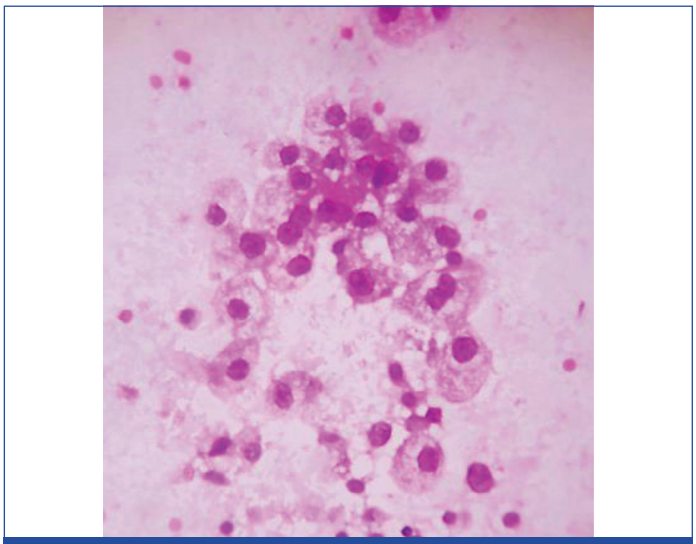


[Table/Fig-1]: Open partial gastrectomy specimen showing a subserosal mass with intact gastric mucosa involving the liver and omentum.
[Table/Fig-2]: Mucosal surface of stomach showing a mass lesion with loss of rugae. (Images from left to right)

Imprint smears were obtained from the fresh specimen and examined. The smears were cellular and showed vacuolated to eosinophilic cells in a non mucinous background [Table/Fig-4]. The differential diagnosis considered were HAC, HCC, and adrenal cortical carcinoma.

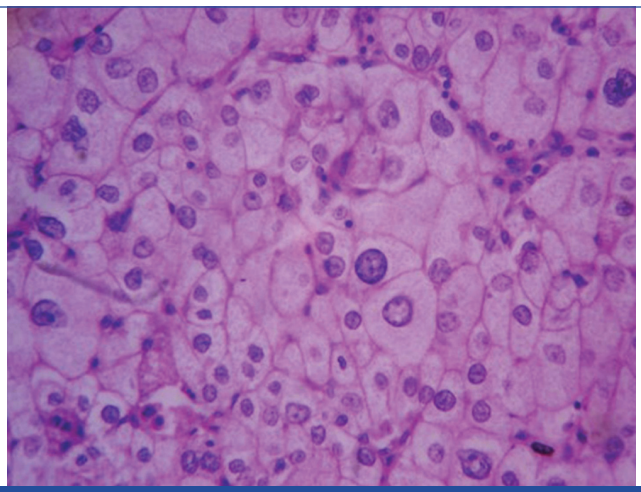


[Table/Fig-3]: Cut surface showed a grey white mass with areas of necrosis and haemorrhage.

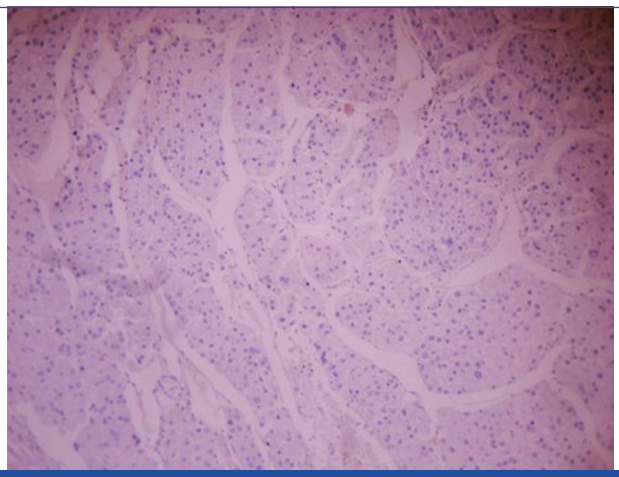


[Table/Fig-4]: Imprint smears showing vacuolated cells in a non mucinous background (H&E stain, 40x magnification).

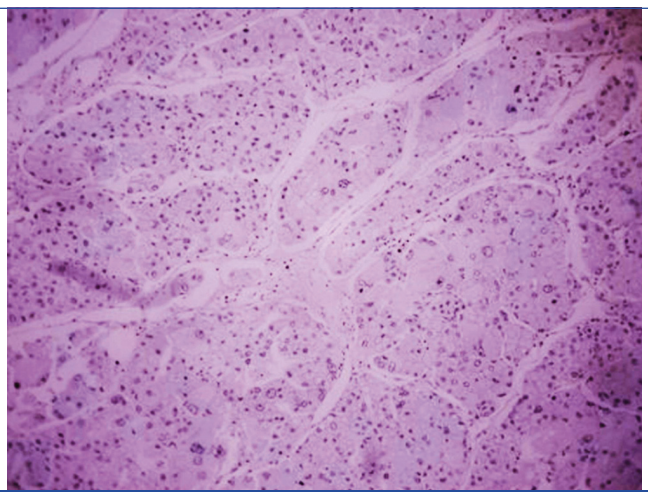
Histopathological examination of the specimen revealed lobules of polygonal cells with abundant eosinophilic to vacuolated cytoplasm and enlarged, moderately pleomorphic nuclei, suggesting hepatoid differentiation [Table/Fig-5]. Immunohistochemistry (IHC) for CD117 [Table/Fig-6] and pCEA were negative [Table/Fig-7], while glypican 3 [Table/Fig-8] and CK 19 were positive. Based on these findings, a diagnosis of HAC was favoured over HCC. Supporting factors for HAC included an elderly male patient, a tumour primarily involving the stomach, aggressive behaviour with invasion into the liver and omentum, absence of risk factors for HCC, negative pCEA, and positive glypican 3 and CK 19. After surgery, the patient was referred to an oncology centre.



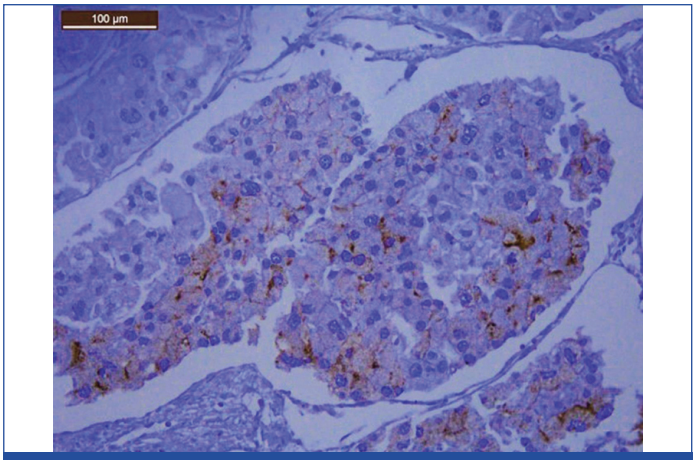
[Table/Fig-5]: Lobules of polygonal cells having abundant eosinophilic to vacuolated cytoplasm with enlarged, moderately pleomorphic nuclei (H&E stain, 40x magnification).



[Table/Fig-6]: Hepatoid Adenocarcinoma (HAC) areas were negative for CD117 (10x magnification).



[Table/Fig-7]: Hepatoid adenocarcinoma areas were negative for pCEA (10x magnification).



[Table/Fig-8]: Hepatoid Adenocarcinoma (HAC) areas showing immunopositivity for Glypican 3 (40x magnification).

DISCUSSION

The first case of HAC was described in 1970 by Bourreille et al., The term "HAC of the stomach" was first proposed by Ishikura et al., in 1985 for gastric tumours that exhibit hepatoid differentiation and high levels of Alpha Fetoprotein (AFP) production. HAC is a distinct type of adenocarcinoma with an extrahepatic origin and has morphological features that overlap with HCC. HACs usually exhibit elevated serum AFP levels, although not always, and they test positive for pCEA and AFP on IHC. The stomach is reported to be the most common extrahepatic site of origin for HAC, and its high frequency in the stomach is attributed to a common origin from the foregut. Other sites of origin include the gallbladder, colon, lung, and urinary bladder. HACs of the stomach are commonly observed in elderly male patients and frequently involve the antrum and body of the stomach [1-3]. HACs are aggressive tumours with a poor prognosis for the patient due to their high frequency of vascular invasion, lymph node involvement, and liver metastasis [4,5]. Differentiating HAC of the stomach with liver metastasis from HCC based solely on clinical presentation, radiology findings, and serological evaluation can be quite challenging. Early diagnosis of HAC of the stomach is crucial for initiation of treatment promptly and improving patient survival [5].

The features that made diagnosis challenging in present study were the unusual subserosal location of the tumour along the greater curvature of the stomach, the fact that AFP levels were not evaluated as HCC or HAC was not suspected, the absence of cirrhosis and risk factors for HCC, confusion regarding the origin of the primary tumour due to its involvement of the liver by direct extension, and the absence of conventional foci of adenocarcinoma. The mural location of the tumour suggested a possible diagnosis of GIST, but the negativity for CD 117 and the absence of characteristic histopathologic features helped us exclude this condition. Although the liver was involved by direct extension, the majority of the tumour tissue was present in the stomach, and there were no risk factors for HCC, which suggested a primary tumour in the gastric region.

HAC shows diffuse staining of the hepatoid elements for carcinoembryonic proteins like AFP, glypican 3, and Sal- like protein 4 (SALL4). Hep-Par 1 and arginase-1 immunostains, which are highly sensitive and specific for HCC, also stain some HAC and hence cannot be helpful in differentiating between HAC and HCC. HACs are noted to stain more frequently for CEA, CK 19, and CK 20 when compared to HCC. Lin 28 is considered to have 98% specificity and helps differentiate HACs from HCC when used in combination with SALL4 [6,7]. IHC findings of the index case showed negative staining for pCEA and positivity for glypican 3 and CK 19, which may be seen in both HAC and HCC.

A final diagnosis of HAC of the stomach was favoured over HCC due to the patient being elderly, the majority of tumour bulk being located in the stomach with invasion into the liver and omentum, the

absence of risk factors for HCC, and negative staining for pCEA but positive staining for glypican 3 and CK 19 on IHC. After surgery, the patient was referred to an oncology centre.

Zeng XY et al., reviewed 328 cases of HAC of the stomach and found that elderly male patients were frequently affected, with a male-to-female ratio of 3.4:1. The most common location of the tumour was the antrum of the stomach, with 78.4% of patients showing lymph node metastasis and 69.6% showing vascular invasion. Among a total of 121 patients, distant metastasis was observed preoperatively, with the liver being the most common site. Survival analysis of 121 cases showed a five-year disease-free survival and disease-specific survival of 20.7% and 29.2%, respectively. The authors also highlight the close association between portal vein thrombosis and disease-free survival of HAC of the stomach [5].

A review of the literature listing the cases of HAC of the stomach published from India is shown in [Table/Fig-9] [8-14].

No.	Authors, place, publication year	Presenting complaint	Age, sex	Immuno negative	Immuno positive
1	Rajasekaran P et al., [8], 2023, Odisha	Pain abdomen	45, Male	AFP, SALL4, MUC2, CD10, and HER2	CK 7, CDX 2, Hep-par1, p53, MUC5AC
2	Sukumaran R et al., [9], 2022, Thiruvananthapuram	Dysphagia, abdominal discomfort	68, Male	CK 7, CK 20	Hep-Par 1, AFP
3	Lakshmanan A et al., [10], 2017, Tamil Nadu	Pain abdomen, generalised weakness	75, Male	PLAP, β- HCG, CD 30	AFP, Gypican, Hep-Par1
4	Gavini S et al., [11], 2017, Tirupati	Pain abdomen, vomiting, loss of apetite	53, Female	-	AFP, α-1-antiptrypsin
5	Mahajan V et al., [12], 2014, Shimla	Pain abdomen, constitutional symptoms	60, Male	Hep Par1	AFP, CK 8, CK 18, CEA
6	Arijit M et al., [13], 2013, West Bengal	Fatigue, generalised weakness, dyspepsia, hematemesis	55, Female	-	AFP
7	Muralee M et al., [14], 2011, Kerala	Pain abdomen, generalised weakness, malena Pain abdomen, Upper GI symptoms	76, Female 60, Male	CK 7, CK 20, CD 30	AFP
8	Present study, 2023, Karnataka	Severe pain abdomen, bilious vomiting and constipation	75, Male	CD 117, pCEA	Glypican 3, CK 19

[Table/Fig-9]: Shows the comparison of present study with other studies [8-14].

CONCLUSION(S)

HAC of the stomach is a rare subtype of gastric carcinoma that frequently affects elderly male patients. It is characterised by an aggressive clinical course and poor survival due to early lymph node metastasis and extensive liver metastasis through the haematogenous route. Several markers such as AFP, CEA, CK 19, Hep-Par1, SALL 4, and glypican 3 may be necessary to differentiate HAC of the stomach from HCC. The diagnosis and treatment of HAC of the stomach pose challenges, and standard surgical and systemic chemotherapy still yield poor outcomes. Therefore, an accurate diagnosis of HAC of the stomach at early stages is crucial to guide treatment options, such as radical surgery and neoadjuvant therapy for patients with lymph node or distant metastasis, in order to improve the prognosis for these patients.

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