

# Hepatic Metastasis from Hepatoid Adenocarcinoma of the Stomach Mimicking Hepatocellular Carcinoma: Diagnostic Challenge

## Abstract

Hepatoid adenocarcinoma (HAC) is a unique type of extrahepatic adenocarcinoma that histologically mimics the appearance of hepatocellular carcinoma (HCC). Hepatoid adenocarcinoma of the stomach has a poor prognosis with increased potential for liver metastasis. HCC and HAC share clinicopathological and immunohistochemical features. The diagnosis of metastatic hepatoid adenocarcinoma to the liver is challenging. It is often misdiagnosed as hepatocellular carcinoma. The diagnostic dilemma is more when the primary tumour is unknown and the first diagnosis is to be established on liver biopsy. Herein, we present the case of a 68-year-old male patient who presented with dysphagia and abdominal discomfort for a three-month duration. Imaging studies showed multiple hypodense lesions in both lobes of the liver. Serum AFP level was markedly elevated to a level of 83,000 ng/ml. A liver biopsy showed atypical polygonal cells in the trabecular pattern. The atypical cells were CK7 negative, CK 20 negative, Hep Par-1 positive and AFP positive. Features were suggestive of hepatocellular carcinoma. Endoscopy showed ulceroproliferative growth in the distal body and antrum of the stomach, a biopsy of which showed atypical cells of similar morphology. The cells were showing focal positivity for CK7, CK20, Hep Par-1 and AFP. On further evaluation, tumour cells in both locations showed positivity for SALL 4. Correlating clinical features, radiology, serum marker values and IHC profile, diagnosis of hepatoid adenocarcinoma of the stomach with liver metastasis was given.

**Keywords:** Adenocarcinoma, Hepatocellular carcinoma, Hepatoid adenocarcinoma, Metastasis, Stomach

## Introduction

Hepatoid adenocarcinoma of the stomach (HAS), is a unique subtype of gastric cancer with specific clinicopathological features. In addition to histological resemblance, HAS and HCC will show positive immunostaining for AFP, Hep Par -1, polyclonal CEA, SALL 4 and Glypican-3. Hepatoid adenocarcinoma of the stomach is characterized by older age, aggressive behaviour and poorer prognosis than usual type adenocarcinoma.<sup>[1]</sup> The aggressive biologic behaviour is due to the early involvement of lymph nodes and extensive haematogenous metastasis to the liver.

The pathogenesis of hepatoid adenocarcinoma is still unclear. Recent studies have demonstrated that the increased incidence of hepatoid adenocarcinoma in the stomach may be due to the common embryonic origin of the stomach and liver from the foregut. The tumour may evolve through genetic progression and/or genetic divergence.<sup>[1-6]</sup>

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The initial presentation of hepatoid adenocarcinoma as liver nodules is challenging, especially in a region with a high prevalence of HCC. Hepatic metastasis from hepatoid adenocarcinoma bears a striking morphologic similarity to HCC. When a patient without any history of hepatitis, liver fibrosis, or cirrhosis present with multiple hepatic nodules with high serum AFP levels, the possibility of metastasis from hepatoid adenocarcinoma should always be considered.<sup>[2]</sup>

## Case report

A 68-year-old male patient presented with dysphagia and abdominal discomfort for a three-month duration. Imaging studies showed multiple hypodense lesions in both lobes of the liver largest measuring 8.4x7.5x5.1cm in segment VII. Another large lesion was noted in segment IVa measuring 6x5cm. Serum AFP was markedly elevated to a level of 83,000ng/ml. A liver biopsy showed atypical cells in a trabecular pattern with surrounding necrosis. Cells were large

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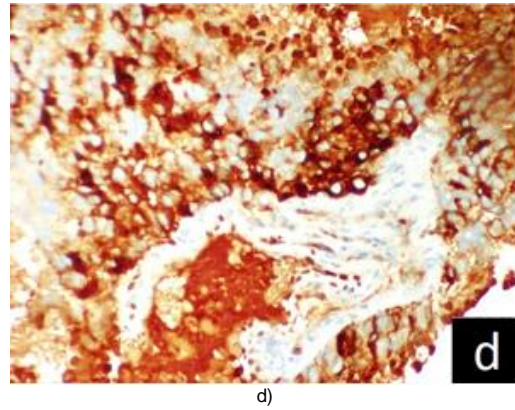
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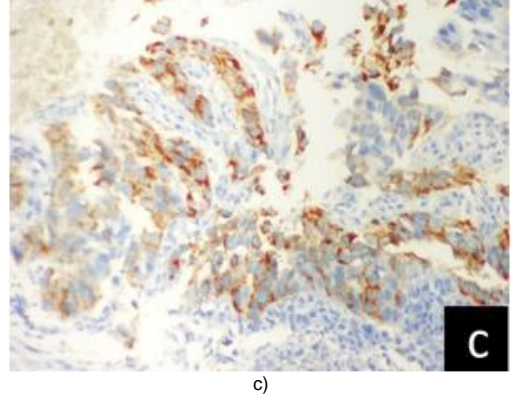
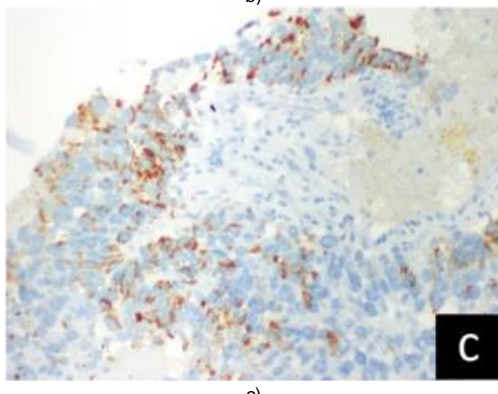
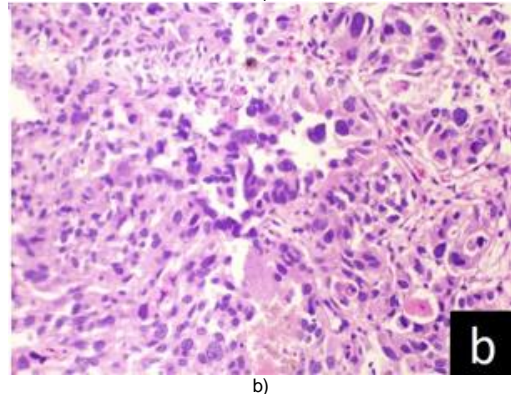
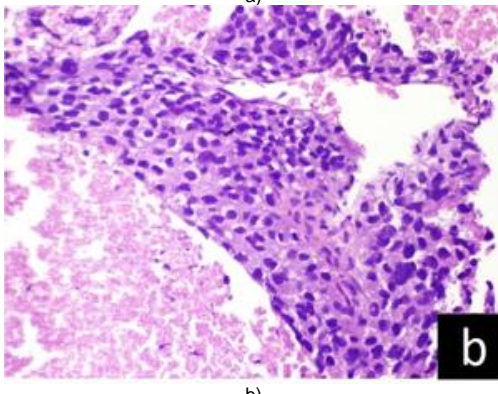
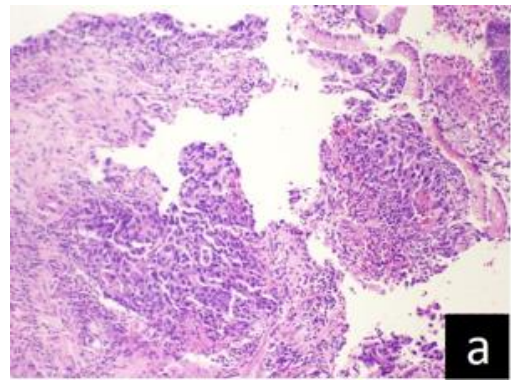
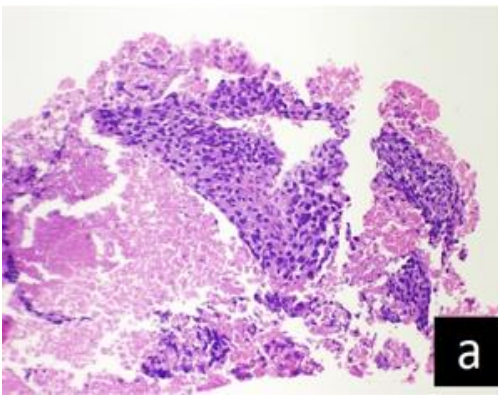
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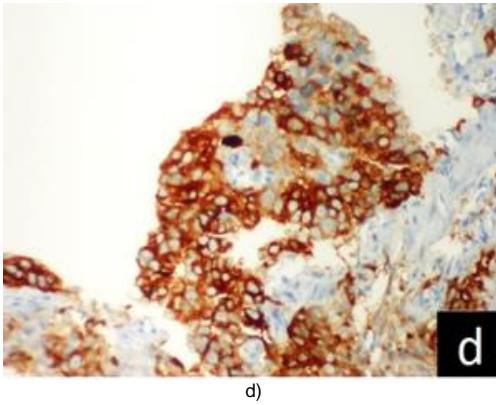


polygonal with moderate to abundant eosinophilic cytoplasm, and enlarged irregular hyperchromatic nuclei (**Figures 1a and 1b**). The atypical cells were CK7 negative, CK 20 negative, Hep Par-1 positive and AFP positive (**Figures 1c and 1d**). Features were suggestive of hepatocellular carcinoma. Subsequent upper GI endoscopy revealed irregular ulceroproliferative growth in the stomach involving the body and antrum. Biopsy showed atypical cells arranged in vague glandular patterns and sheets, morphology was similar to the cells in liver biopsy (**Figures 2a and 2b**). The cells were showing positivity for CK7, CK20, Hep Par-1 and AFP (**Figures 3a, 3b, 2c and 2d**). Neoplastic cells in both locations showed positivity for SALL4 (**Figures 3c and 3d**). Correlating clinical features, radiology and serum marker values, a diagnosis of hepatoid adenocarcinoma of the stomach with liver metastasis was given.



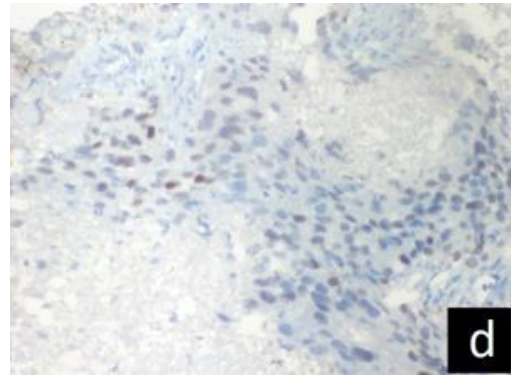
**Figure 1.** a) Liver biopsy showing large atypical cells surrounded by necrosis (H&E, 100X), b) Higher magnification showing large atypical polygonal cells (H&E, 200X), c) Neoplastic cells showing positivity for Hep par-1 (IHC, 200X), d) AFP positivity (IHC, 200X)





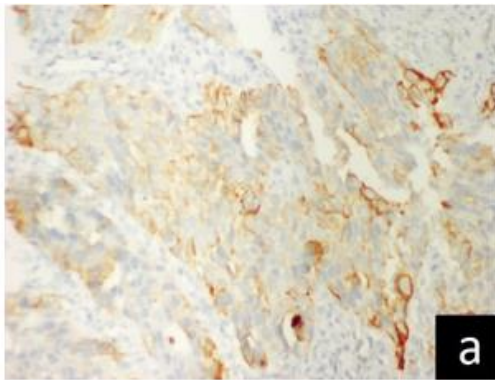
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**Figure 2.** a) Gastric biopsy showing infiltrating neoplasm (H&E, 100X), b) Higher magnification showing atypical cells arranged in vague glandular pattern and in sheets (H&E, 200X), c) Neoplastic cells showing positivity for Hep par-1 (IHC, 200X), d) AFP positivity (IHC, 200X).

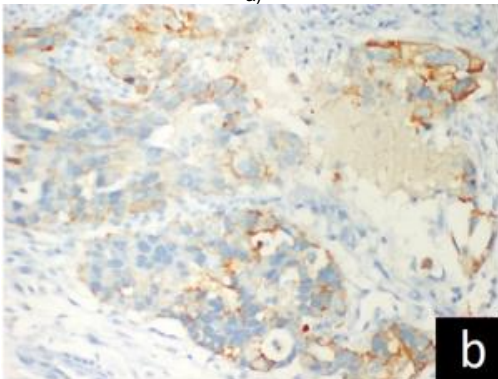


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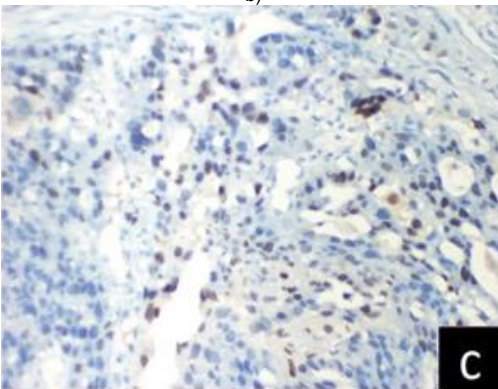
**Figure 3.** a) Neoplastic cells in gastric biopsy showing patchy positivity for CK7, b) patchy positivity for CK20, c) Focal positivity for SALL 4 in neoplastic cells in the gastric biopsy, d) Atypical cells in liver biopsy showing focal positivity for SALL4 (IHC, 200X)



a)



b)



c)

## Results and Discussion

Hepatoid adenocarcinoma of the stomach (HAS) is a rare and aggressive neoplasm. It is characterised by distinctive foci of hepatocellular differentiation, composed of large, polygonal cells with abundant eosinophilic cytoplasm that often produces alpha-fetoprotein (AFP). It occurs in the older age groups ranging from 49 to 78 years.<sup>[1, 3-5]</sup>

Metastasis to the liver is common in hepatoid adenocarcinoma of the stomach. The initial presentation of HAS as liver nodules poses a diagnostic challenge because of the similarity in morphology and immunoprofile. The diagnostic confusion is more when it occurs in a region with a high prevalence of HCC.<sup>[2]</sup>

The first case of hepatoid adenocarcinoma was described by Bourreille *et al.* in 1970. Ishikura *et al.* proposed the term ‘hepatoid adenocarcinoma of the stomach.’<sup>[2]</sup>

Hepatoid adenocarcinoma of the stomach (HAS) exhibits mixed tubular and/or papillary patterns with distinct hepatoid areas. HAS exhibits a strong tendency for liver and lymph node metastases and has aggressive bio-behaviour.<sup>[4]</sup> Rare cases with metastasis to the brain and spleen are also reported.<sup>[6, 7]</sup> Hepatoid component of HAS can be more prominent in metastatic lesions in the liver and perigastric nodes.

## Pathogenesis

The pathogenesis of hepatoid adenocarcinoma is still unclear. It is reported in the stomach, oesophagus, colon, lung, pancreas, peritoneum and ovary. Foregut derivation of the liver and stomach could be the likely reason for the increased incidence in the stomach. However, the exact molecular mechanism of HAS is unclear.<sup>[1, 8, 9]</sup> It is postulated to be due to cellular trans-differentiation from glandular to hepatoid type.<sup>[10]</sup> In their study, Akiyama *et al.* demonstrated that the hepatoid component and the conventional adenocarcinoma component of hepatoid adenocarcinoma exhibited the same patterns of chromosome X inactivation, p53 gene mutation, the

level of p53 expression, and loss of heterozygosity. They suggested a monoclonal origin of both glandular and hepatoid elements of HACS. These findings support “transdifferentiation” as the most accepted histogenesis of hepatoid adenocarcinoma.<sup>[8]</sup>

Studies have demonstrated the hepatoid component in hepatoid adenocarcinoma was present only in invasive areas indicating the HAS originated as common gastric cancer in the mucosa and differentiates into HAS during the process of tumour invasion. The study by Akiyama *et al.* showed that the higher the HAS cell component percentage in a tumour, the more AFP secreted by the tumour.<sup>[8]</sup>

### Diagnosis

The histological findings of hepatoid adenocarcinoma in the stomach usually reveal adenocarcinoma with foci of hepatoid differentiation showing solid, trabecular and pseudo glandular arrangement. Large polygonal tumour cells with prominent cell borders, abundant eosinophilic cytoplasm, central nuclei and prominent nucleoli are the characteristic features of hepatoid foci. High proliferative activity and rich neovascularization indicate the high-grade malignant potential of this neoplasm. The immunohistochemical staining pattern has been variably reported in the literature. The tumour usually shows positivity for alpha-fetoprotein, polyclonal CEA, CK 8 and CK 18. Recent studies have demonstrated positive staining of Glypican-3, SALL4, and Hep Par -1 in a proportion of cases.

Alpha-fetoprotein is a marker related to embryonic development mainly used for diagnosing germ cell tumours especially yolk sac tumours and liver tumours such as hepatoblastoma and hepatocellular carcinoma. Nonneoplastic conditions of the liver such as hepatitis and cirrhosis with associated regenerative changes can result in elevated serum AFP levels. Malignant tumours with hepatoid differentiation showing elevated serum AFP levels and AFP positivity on the immunohistochemical examination have been reported in different organs such as the stomach, lung, pancreas, colon, ovary and urinary bladder.

Hep Par- 1 is considered the most sensitive and specific IHC marker for hepatocyte differentiation. In hepatocellular carcinoma, the reported sensitivity of Hep Par- 1 is 82% and specificity is 90%.<sup>[11]</sup> Literature search shows focal positivity for Hep Par-1 in 13% to 85% of carcinoma with hepatoid differentiation.<sup>[11-13]</sup> The presence of Hep Par 1 reactivity in extrahepatic hepatoid adenocarcinomas points to the fact that adenocarcinoma with hepatoid features must be considered in the differential diagnosis of Hep Par-1positive lesions. The present case showed positive staining for Hep Par -1 in both hepatic and gastric tumours.

SALL4 is expressed in the foetal liver, its expression declines gradually during development and is silenced in adulthood. Re-expression of SALL4 is recognized in various cancers and is considered an adverse prognostic factor in HCC, breast cancer, and lung cancer. Studies have demonstrated SALL4

expression in 94.7% of hepatoid adenocarcinoma of the stomach and 10.5% of common gastric carcinoma.<sup>[1, 14]</sup>

A study by Wang *et al.* demonstrated copy number gains (CNGs) at 20q11.21-13.12 occurred frequently in HAS. This CNG tended to be related to more adverse behaviour.<sup>[1]</sup>

### Conclusion

Due to its rarity and aggressive behaviour, pathologists need to be aware of hepatoid adenocarcinoma to make a correct diagnosis. Diagnosis is challenging when the tumour has already metastasized to the liver and resembles hepatocellular carcinoma, both morphologically and clinically. The diagnosis of HAS should be considered in case of multiple hepatic tumours with elevated AFP, especially in patients with no evidence of chronic liver disease. In such a scenario, the performance of an upper gastrointestinal endoscopy should be considered to rule out HAS.

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### Conflict of interest

None.

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None.

### Ethics statement

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for images and other clinical information to be reported in the journal. The patient understands that their name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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