

Hepatoid Adenocarcinoma of Gallbladder: A Mimicker of Hepatocellular Carcinoma

Sir,

Hepatoid adenocarcinoma (HAC) is a rare carcinoma showing hepatocellular differentiation, arising in extrahepatic organs. This tumor was initially reported as an alpha-fetal protein (AFP)-producing tumor of gastric origin in 1970.^[1] Later, Ishikura and Scully^[2] proposed the term “hepatoid carcinoma” for AFP-producing ovarian adenocarcinoma in 1987. Nearly 408 HAC cases of HAC arising from different origins have been reported till date.^[3] They are more common in the stomach compared to other parts of GIT.^[3] Their occurrence in the gallbladder is rare.^[3-7] We report one such rare occurrence in the gallbladder of a 60-year-old female who presented with a complaint of pain in the right hypochondrium for 3 months. Ultrasonography revealed cholelithiasis and an enlarged peripancreatic lymph node. CECT abdomen revealed a focal heterogeneously enhancing thickening of the gallbladder wall with abdominal lymphadenopathy. The liver was within normal limits. Radiological findings were suspicious for malignancy.

Cholecystectomy was done, and we received the specimen of the gallbladder which grossly revealed a polypoidal exophytic growth measuring 1.5 cm × 1 cm × 0.5 cm [Figure 1]. Cut section of the growth was gray white and extending into the serosa. Microscopic examination revealed sheets, nests, and trabecular cords of tumor cells [Figure 2] with focal glandular pattern in superficial lamina propria. These tumor cells revealed round to irregular enlarged vesicular nuclei, prominent one to multiple nucleoli, and abundant finely granular eosinophilic cytoplasm with distinct cytoplasmic border. Occasional hyaline globules and intranuclear inclusions, atypical mitosis, and focal necrosis were seen.

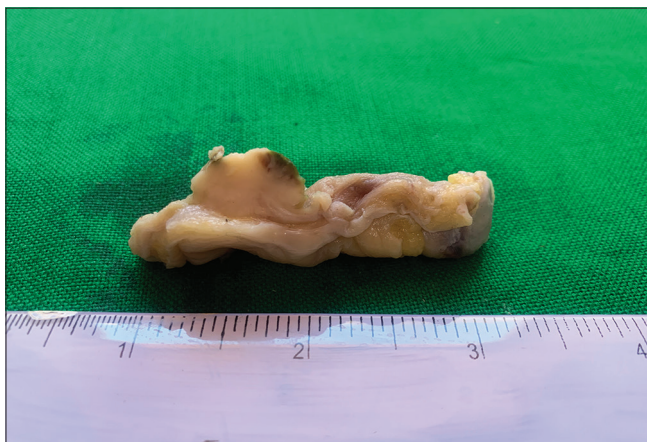


Figure 1: Gross specimen showing polypoidal exophytic growth in the gallbladder

Mucosa adjacent to the growth revealed adenocarcinoma *in situ* [Figure 3]. A diagnosis of HAC of the gallbladder was made, and immunohistochemistry was positive for AFP but negative for HepPar1.

HACs most commonly arise from the stomach. Less commonly, they arise from the ovary, lung, pancreas, and rarely, in the uterus, esophagus, jejunum, colon, rectum, gallbladder, or extrahepatic bile duct.^[3] Vardaman and Albores-Saavedra^[8] described the first well-documented case of HAC of the gallbladder, and subsequently, to the best of our knowledge, approximately 15 cases have been reported in the English literature.^[3-7]

The diagnostic criteria for defining “hepatoid carcinoma” have been variable in practice. Some consider elevated serum AFP as a defining feature of hepatocellular differentiation, and others rely on morphological features of hepatocyte. Hepatoid differentiation manifests as large polygonal cells with abundant clear and eosinophilic cytoplasm that are arranged in trabeculae, nests, and rosettes. The hepatoid nature of the tumor cells is demonstrated by bile production.^[9] Some others have reported the immunohistochemical expression of hepatocellular markers including AFP, HepPar1, glypican-3, arginase, albumin, or Sall-4 in tumor cells.^[9,10]

AFP positivity in tumor cells is particularly important for diagnosis. AFP levels are also elevated in the serum. However, HAC does not always produce AFP.^[11-13] Although AFP positivity is important, it is not essential for a diagnosis of HAC. The diagnosis of HAC should be made on the basis of histopathological features of the tumor including immunohistochemical analysis, because the behavior of HAC is similar whether it produces

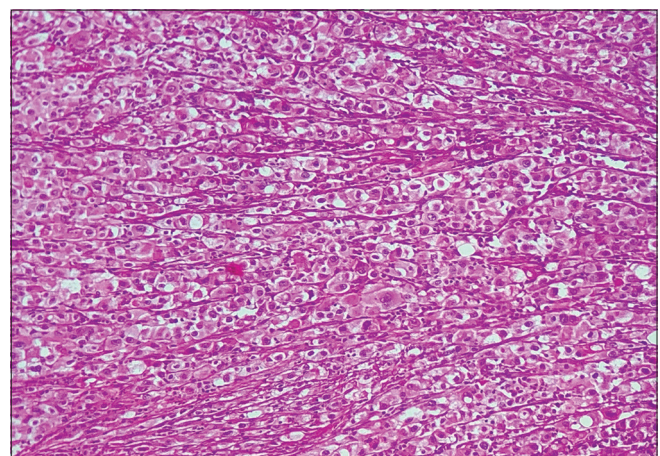


Figure 2: Hepatoid tumor cells arranged in trabecular pattern (H and E, ×20)

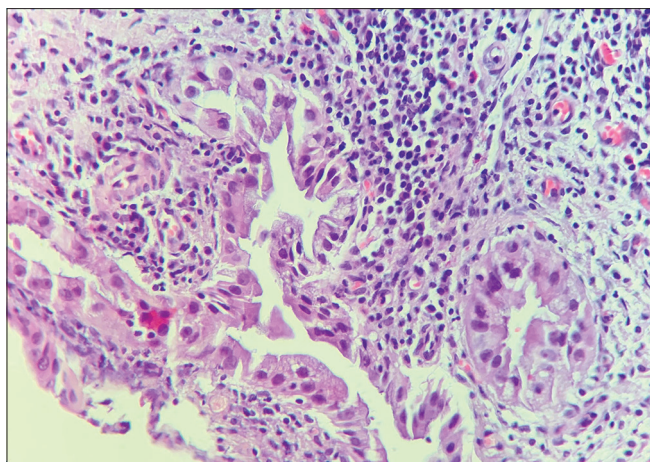


Figure 3: Foci of adenocarcinoma in superficial lamina propria (H and E, ×40)

AFP or not.^[11] HepPar1 has been used as a marker of hepatic differentiation, but subsequent studies have refuted its specificity and sensitivity. In this case, AFP was positive [Figure 4], but HepPar1 was negative. The main differential diagnosis for HAC of the gallbladder is hepatocellular carcinoma (HCC) or combined HCC/cholangiocarcinoma invading the gallbladder. The clinical presentation of patients is important because HCC arising in nonfibrotic liver and without risk factors, such as hepatitis virus infection, is generally rare, as is lymph node metastasis at surgery. If the intramucosal foci of adenocarcinoma are detected histologically in a surgical specimen, the gallbladder origin is confirmed.^[12] In our case, the gallbladder origin of the HAC was confirmed as there was a focus of adenocarcinoma and high-grade dysplasia/carcinoma *in situ* in the adjacent epithelium and the absence of cirrhosis.

HAC occurs predominantly in older patients and is characterized by a very aggressive course and a poor prognosis. Extensive hematogenous metastasis to the liver and the early and frequent involvement of lymph nodes is an important feature.^[13]

Conclusion

Although HAC of the gallbladder is a very rare malignancy, awareness of its existence is critical to avoid misdiagnosis and these tumors should be considered in the differential diagnosis of gallbladder masses.

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Conflicts of interest

There are no conflicts of interest.

Kavita Mardi, Monica Sarohi

Department of Pathology, Indira Gandhi Medical College, Shimla,
Himachal Pradesh, India

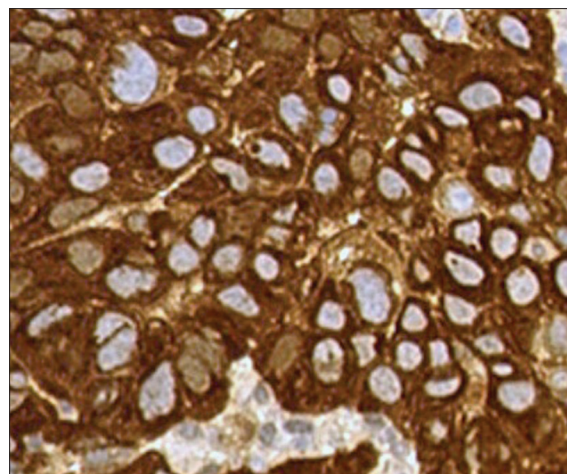


Figure 4: Tumor cells showing positivity for alpha-fetal protein (Immunohistochemistry, ×40)

Address for correspondence: Dr. Kavita Mardi,
Set No 14, Type VI Quarters, IAS Colony, Meheli, Shimla, Himachal
Pradesh, India.
E-mail: kavitamardi@yahoo.co.in

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