Hepatoid Carcinomas (Adenocarcinomas with Hepatoid Features)

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Abstract

Hepatoid carcinoma (adenocarcinoma with hepatoid features) is a highly aggressive carcinoma occurring in various organs, morphologically characterized by the presence of HCC-like cells that frequently express alpha-fetoprotein, but with a cytokeratin pattern that differs from that of classical HCC, in that tumor cells are often positive for cytokeratins 7 and 20. Similar to HCC, gastrointestinal hepatoid carcinomas can express the hepatocyte marker Hep Par 1. These neoplasms are associated with rapid progression and a poor outcome. Most hepatoid carcinomas found in the liver are metastases of gastric hepatoid carcinomas, the stomach being a frequent primary site. Primary hepatoid carcinomas also occur in bile ducts, the gallbladder, and the ampullary region, but these are uncommon locations. The histogenesis of this neoplasm has not yet been elucidated.

Introduction

Some carcinomas occurring in several organs, but in particular the gastrointestinal tract, can show signs of hepatocellular differentiation, either focally or almost exclusively. These lesions, which are termed hepatoid (adeno)carcinomas or extraheptic tumors with hepatoid features (EHTHF), may be associated with elevated serum AFP levels and an aggressive course

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_17

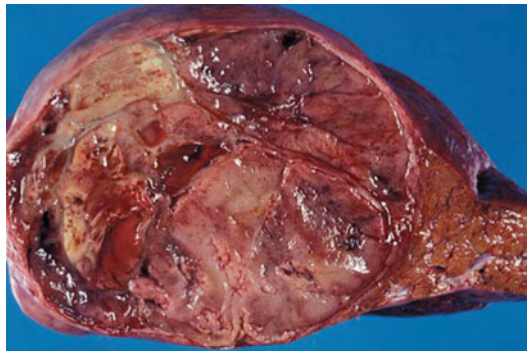

Fig. 1 Hepatoid carcinoma of the liver. These are rapidly growing, aggressive neoplasms developing in non-cirrhotic livers

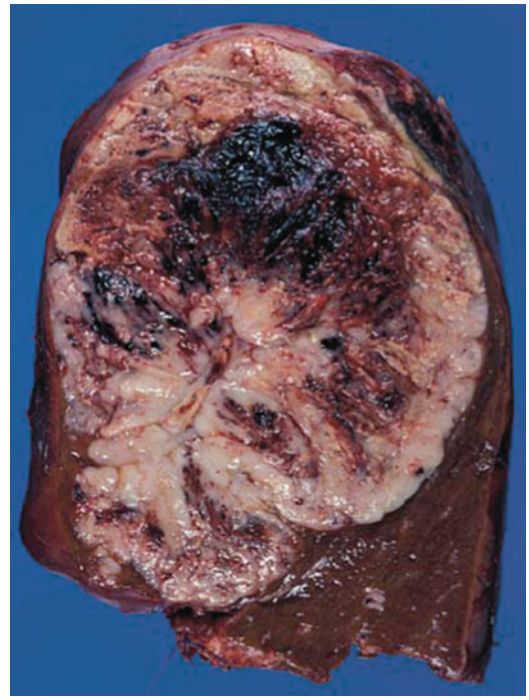

Fig. 2 The macroscopic morphology of hepatoid carcinomas of the liver resembles that of carcinoma metastases. Necrosis and hemorrhages are common features

(reviews: Kishimoto et al. 2000; Su et al. 2013). Typical primary sites of these carcinomas include the stomach (the most common site), esophagus, pancreas, gallbladder, colon, lung, ovary, urinary bladder, renal pelvis, uterus, fallopian tube, and adrenal gland. Hepatoid carcinomas usually have a distinct and unique immunophenotype, characterized by reactivity for cytokeratins 7, 8, 18, 19, and 20, alpha-fetoprotein (AFP), and pCEA (Terracciano et al. 2003). Immunoreactivity for AFP is variable, ranging from absence of staining to marked and diffuse staining of cancer cells, illustrating that not all carcinomas with a hepatoid morphology are producing AFP (Nagai et al. 1993). Many hepatoid carcinomas of the gastrointestinal tract show, similar to hepatocellular carcinomas, reactivity for hepatocyte paraffin 1 (Hep Par 1) antibody, underscoring the fact that Hep Par 1 expression is not unique to primary hepatocellular neoplasms (Maitra et al. 2001). At least part of hepatoid carcinomas are positive for glypican-3, a cell surface heparin sulfate proteoglycan expressed specifically in the fetal liver and in malignant neoplasms of the hepatocyte lineage (Hishinuma et al. 2006). Generally, hepatoid carcinomas are highly aggressive tumors (Figs. 1 and 2).

For example, it has been demonstrated that AFP-producing gastric carcinoma and hepatoid adenocarcinomas of the stomach had a more aggressive biology than that of common gastric cancer and that the prognosis of hepatoid tumors was poorer than that of AFP-producing gastric carcinoma (Liu et al. 2012).

Histologically, hepatoid carcinomas consist of large or medium-sized polygonal cells that are arranged in trabecular fashion or solid nests separated by narrow fibrous stroma bands and sinusoid-like channels (Fig. 3).

Rarely, hepatoid carcinomas showed, apart from the predominant adenocarcinoma, other components, e.g., endocrine carcinoma (Suzuki et al. 2012). It is often difficult to distinguish EHTHF from metastatic hepatocellular carcinoma (HCC) using any kinds of ancillary studies, with the exception of clinical-radiological identification of a hepatic tumor (Kwon et al. 2006).

Some of the extrahepatic carcinomas with morphological resemblance to hepatocellular carcinoma are AFP-negative, but may show positive signals for albumin mRNA in ISH preparations (Supriatna et al. 2005). On the other hand, it has to be emphasized that the mere presence of immunohistochemical markers known to be expressed

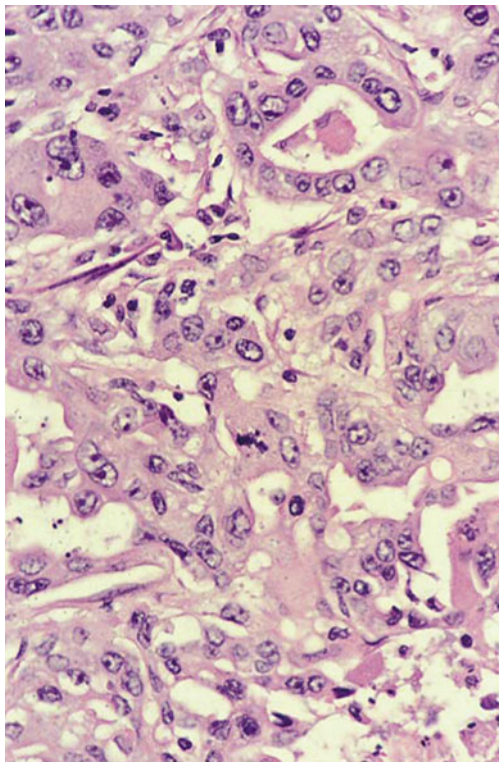

Fig. 3 Hepatoid carcinoma in the liver. The neoplasm consists of cells similar to those in hepatocellular carcinoma, but tubular structures are also encountered, and the tumors are often pleomorphic, with highly atypical nuclei and abnormal mitotic figures (hematoxylin and eosin stain)

in hepatoid cell lineages does not mean that we deal with EHTHF. It has, e.g., been shown that hepatoid carcinoma of the gastrointestinal tract (Maitra et al. 2001) and diverse types of cervical carcinomas (including ordinary adenocarcinoma, adenocarcinoma in situ, and squamous cell carcinomas) can be reactive for Hep Par 1 (Thamboo and Wee 2004) and that Hep Par 1 does not distinguish between EHTHF of the ovary from metastatic HCC (Pitman et al. 2004). AFP-producing adenocarcinoma without morphological hepatoid features may also be positive for glypican 3 (Hishinuma et al. 2006; Oishi et al. 2009). SALL4, a stem cell marker and a marker for fetal gut differentiation, is expressed in the majority of gastric EHTHF, but not in HCCs (Ushiku et al. 2010). On a molecular level, it has been found that foci of hepatoid differentiation in EHTHF show restricted expression of hepatocyte nuclear factor 4 alpha (Kishimoto et al. 2008). Expression of the PLUNC (palate, lung, and nasal epithelium carcinoma-associated protein) gene is a marker for EHTHF (Sentani et al. 2008). PLUNC, also termed lung-specific X protein (LUNX), is a major secreted protein product of the upper respiratory tract, of a still unknown function.

Hepatoid Carcinomas of the Extrahepatic Biliary Tract

Primary EHTHF of the extrahepatic ducts are very rare lesions. In one case, a 67-year-old female suffering from obstructive jaundice had a stenosing mass at the common hepatic duct, mimicking a Klatskin tumor, histologically representing hepatoid carcinoma. The tumor was associated with elevated serum AFP levels (Abdullah et al. 2010). A hepatoid tumor located to the common duct showed all immunohistochemical features characteristic for EHTHF, i.e., positivity for Hep Par 1, CK8, and CK18 (Wang et al. 2013).

Hepatoid Carcinoma of the Gallbladder

EHTHF is known to occur in the gallbladder (Watanabe et al. 1993; Vardaman and Albores-Saavedra 1995; Nishiwaki et al. 1997; St Laurent et al. 1999; Nakashima et al. 2000; Maitra et al. 2001; Sakamoto et al. 2004, 2005; Gakiopoulou et al. 2007; Koswara et al. 2007: van den Bos et al. 2007; Kao et al. 2009; Ellouze et al. 2011). The tumors may be associated with elevated serum AFP levels (van den Bos et al. 2007). In principle, the neoplasms show the same histologic features as those in other locations. Macroscopically, the tumors however often differ from ordinary gallbladder carcinoma by their more nodular and sometimes polypoid growth pattern. In one case of Sakamoto et al. (2005), a 74-year-old female with a long history of cholecystolithiasis exhibited a nodular and elevated gallbladder tumor of 5 cm diameter,

consisting of AFP-positive and Hep Par 1-positive hepatoid cells. Part of the tumors showed cholangiocarcinoma-like components, which also immunostained for AFP (Koswara et al. 2007). In a case reported in 1995, the AFP-producing tumor belonged to the group of clear cell carcinomas of the gallbladder (Vardaman and Albores-Saavedra 1995). Gallbladder carcinomas associated with elevated serum AFP levels are not always hepatoid lesions, but may instead represent other histologies, e.g., standard adenocarcinoma (Brown and Roberts 1992) or undifferentiated carcinoma (Ng and Ng 1995).

Hepatoid Carcinoma of the Ampullary Region

Few cases of primary hepatoid carcinoma of the ampullary/periampullary region have been described (Gardiner et al. 1992; Weng et al. 2009; Palas et al. 2013). The tumor described by Gardiner and co-workers (1992) was located to the papilla of Vater and consisted of a poorly differentiated adenocarcinoma with clear cells containing occasional hyaline droplets and exhibiting bile secretion. Immunohistochemically, AFP, alpha-1-antitrypsin, and CEA were detectable.

Liver Metastasis of Hepatoid Carcinomas

Hepatoid carcinoma of the stomach, the most common localization for this tumor, relatively often metastasizes to the liver, but also other primary intra-abdominal localizations give rise to hepatic metastatic disease (Yoshida et al. 2005; Jo et al. 2012). EHTHF with liver metastasis may mimic HCC (Pan et al. 2011; Jo et al. 2012; Moon et al. 2012), but EHTHF metastases are more commonly positive for CK19 and CK20 and are more often negative for Hep Par 1 than HCCs (Terracciano et al. 2003).

Differential Diagnosis

The main differential diagnoses include metastatic hepatocellular carcinoma and germ cell tumors with marked hepatoid differentiation. HCCs are known to show unusual metastasizing patterns and can, e.g., metastasize to the gallbladder, causing a lesion pattern that may not be distinguishable from primary hepatoid carcinoma (Terasaki et al. 1990). Apart from AFP, embryonal carcinoma has been found to secrete des-gamma-carboxy prothrombin (Hasegawa et al. 2005).

Pathogenic Pathways

Novel observations on the lineage relationships between pancreatic cells and hepatocytes, and their respective precursors, may shed a light on pathogenic mechanisms involved. Of course the liver and the pancreas ontogenically derive from a similar fated endodermal area, but this will not suffice for the understanding of carcinogenic pathways. A key molecule involved in the prenatal development of the stomach and liver is the transcription factor, GATA4. In AFP-producing gastric carcinoma cells, GATA4 expression is silenced via epigenetic histone deacetylation (Yamamura and Kishimoto 2012). Gastric carcinoma producing AFP was shown to share the main histologic features with combined hepatocellular and cholangiocarcinoma, but revealed a different histogenesis with respect to SALL4 expression. Specifically, the germ cell marker SALL4 was expressed in 95 % of AFP-producing gastric carcinomas, including those with a hepatoid component, but was not detectable in combined hepatocellular and cholangiocarcinoma (Ikeda et al. 2012).

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