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COMMUNICATION

Hepatoid Adenocarcinoma of the Colon: What Should We Target?

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Abstract Hepatoid adenocarcinoma is a rare extra hepatic neoplasm that displays morphological and phenotypic features similar to those of hepatocellular carcinoma. We report a case of a 75-year-old woman, presenting with abdominal pain and complaints of weakness and lost of appetite, who was found to have a mass on her right colon. She underwent right hemicolectomy for a pT3N2M0, stage IIIC colon cancer. The tumor phenotype and immunophenotype, as documented by alpha-fetoprotein immunoreaction positivity, were consistent with adenocarcinoma of hepatoid origin. The patient received FOLFOX-4 regimen as adjuvant treatment, relapsed after six cycles, then was switched to FOLFIRI regimen plus Bevacizumab and progressed after only four cycles. She died 1 month later, eight months after the diagnosis. The lack of any clinical benefit despite an aggressive and multimodal therapeutic strategy, raises a question about what should be targeted when we face this rare disease associated with a very poor prognosis.

Keywords Hepatoid adenocarcinoma · Colon cancer · Hepatocellular carcinoma · Alpha-fetoprotein · FOLFOX · FOLFIRI

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Introduction

In 1970, Bourreilile et al [1] first described a case of liver metastasis from gastric adenocarcinoma with increased alpha-fetoprotein (AFP) in the serum. Fifteen years later Ishikura et al [2], reporting an analogue case, proposed the concept of "hepatoid carcinoma." Since then, cases of adenocarcinoma with features mimicking hepatocellular carcinoma have been described.

Hepatoid adenocarcinoma is a rare extra hepatic neoplasm that displays morphological and phenotypic features similar to those of hepatocellular carcinoma [3, 4]. It has been mostly reported in the stomach (63%), but sporadic cases have also been described in the ovaries (10%), lung (5%), gallbladder (4%), pancreas (4%), and uterus (4%) [5]. Patients with inflammatory bowel disease (IBD) have an increased risk of developing intestinal malignancy. Four out of seven cases of hepatoid adenocarcinoma of the intestine reported in the literature are associated with IBD [6–8]. This neoplasm has a poor prognosis, frequently presents at an advanced stage, and usually with liver metastases; AFP overproduction happens in most but not all cases and it may help direct the diagnosis when it is elevated. To our knowledge, no mention about treatment of hepatoid adenocarcinoma arising from the colon-rectum has been reported in the literature. Herein, we describe the case of a colorectal adenocarcinoma with hepatoid features, slight increase of AFP and resistance to standard chemotherapy used for colorectal cancer.

Case Report

A 75-year-old woman presented with abdominal pain, complaints of weakness and loss of appetite during the

past 3 months. The patient had no remarkable medical history, except for osteoporosis, uterine fibromatosis and high cholesterol. Apart from abdominal tenderness, review of systems and physical examination were not relevant. Chest and abdominal computed tomography (CT) revealed an irregular thickening of ascending colon walls with mesenteric lymphadenophaty. The liver did not show any space-occupying lesion. Laboratory values were within normal limits, including CEA and CA 19–9. Serum AFP was not assessed preoperatively. Colonscopy showed a large, vegetating, mostly necrotic mass near the ileo-cecal valve and a biopsy confirmed it being an adenocarcinoma. The patient underwent right hemicolectomy with ileo-colic anastomosis. Gross morphology showed a 6 cm diameter infiltrating neoplasm. Four out of 12 dissected lymph nodes were metastatic. Fenotype and immunofenotype, as documented by alpha-fetoprotein immunoreaction positivity, were consistent with hepatoid origin. The final diagnosis was poorly differentiated hepatoid adenocarcinoma of the colon with nodal involvement (pT3N2M0, stage IIIC).

On hematoxylin and eosin-stained slices, tumor cells showed large polyhedral cells in a trabecular and gland-like pattern (Fig. 1a, b). Some cancer cells showed empty spaces as on hepato-steatosis (Fig. 1c). Immunohistochemically, the cancer cells showed cytoplasmic positivity for alpha-fetoprotein (Fig. 1d). The tumor cells were negative for the hepatocyte specific marker hepatocyte paraffin-1 (Her Par-1) and for Glypican 3 (GPG3). These immunohistochemical findings combined with the morphological features described above, supported the diagnosis of hepatoid variant of colorectal adenocarcinoma.

The patient received fluorouracil, leucovorin and oxaliplatin biweekly (FOLFOX-4 regimen) as adjuvant treatment. The chemotherapy was well tolerated even though she kept suffering from abdominal pain despite taking mild analgesics. After 3 months (six cycles) of chemotherapy, a CT scan revealed a retroperitoneal mass 4 cm in diameter, extensively necrotic and infiltrating the head of the pancreas (Fig. 2a). At that time laboratory investigation showed a very slight increase of AFP up to 8.5 ug/L (N.V.: 0.0-7.0). No other parameter was out of range apart from elevated lactic dehydrogenase (1031 U/L). Therefore, she started first-line chemotherapy for metastatic disease with biweekly fluorouracil, leucovorin and irinotecan (FOLFIRI regimen) plus bevacizumab (Avastin ®, Roche-Genetech). Two months later, after four cycles, a new CT scan showed an increase in size of the retroperitoneal mass up to 78× 55 mm (Fig. 2b), and also appearance of bilateral pleural effusion, mild ascites and left subclavian lymphadenopathy. The patient was considered out of any further chemotherapy treatment and continued with basic supportive care. She died 1 month later, eight months after the diagnosis.

Discussion

We present herein a case of hepatoid adenocarcinoma of the colon. This rare tumor has been reported in various organs, the stomach being the most prevalent site. This preponderance in the stomach has been attributed to the common embryologic derivation of the liver and the stomach from the foregut. The other anatomic locations also include

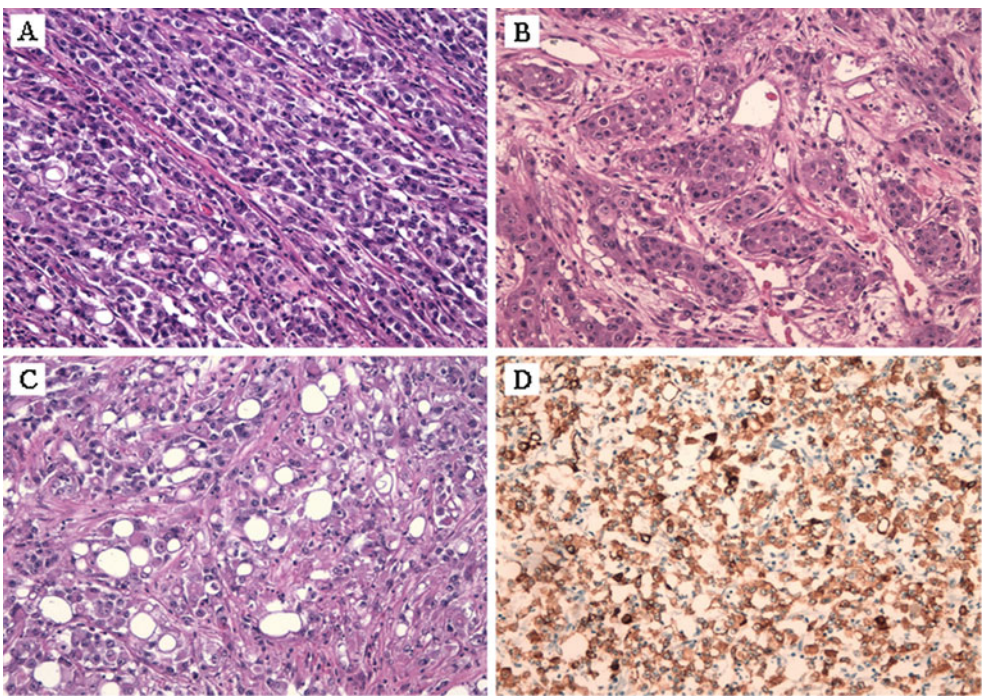

Fig. 1 Hispathology. **a**, **b**. Poorly differentiated colorectal adenocarcinoma composed of poligonal cells organized in trabecular sheets strictly resembling an hepatocellular (Hematoxillin-Eosin, original magnification × 200). **c**. Some cancer cells show vesicular empty spaces resembling steatosis (Hematoxillin-Eosin, original magnitification × 200). **d**. Immunohistochemical cytoplasmic positivity for α1 fetoprotein (immunohistochemistry, original magnification × 200)

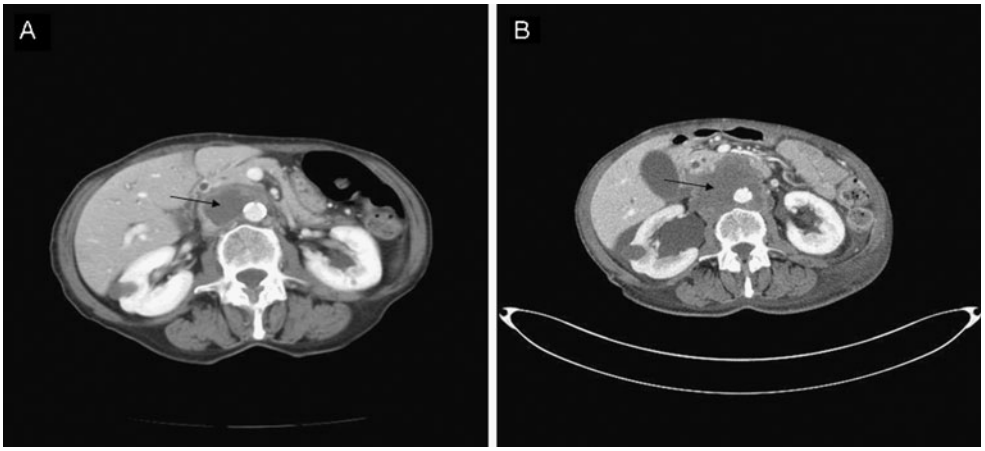

Fig. 2 CT images. **a**. After 3 months (six cycles) of adjuvant chemotherapy, a CT scan revealed a retroperitoneal mass 4 cm in diameter, extensively necrotic and infiltrating the head of the pancreas. **b**. Two months later, after four cycles of chemotherapy for metastatic disease, a new CT scan showed an increase in the size of the retroperitoneal mass up to 78×55 mm

colon-rectum, where it has showed an apparently strong correlation with inflammatory bowel disease. No known genetic basis has been elucidated to predispose to intestinal malignancy in IBD, and it has been postulated that the chronic inflammation may play a crucial role. Although the causal relationship between IBD and hepatoid carcinoma is not well understood, notably four out of seven cases of hepatoid adenocarcinoma of the intestine reported in the literature thus far have been associated with IBD.

In this neoplasm, AFP overproduction happens in most but not all the cases and may help direct the diagnosis. We do not usually measure AFP for the preoperative diagnosis of colorectal cancer. Only the postoperative histopathologic results cause us to measure the AFP level. It was slightly increased in our patient, but neither fell to normal value after chemotherapy nor rose when disease progressed. Therefore, in our case AFP was a useless marker for therapeutic response evaluation and potentially also for diagnostic purposes.

The pathogenesis of hepatoid tumors is not fully understood. There are several unanswered questions about the biology of these tumors. First, this tumor displays a high angioinvasiveness [3]. This feature of aggressiveness, shared with few other kinds of epithelial neoplasia such as hepatocellular and renal carcinoma, could partially explain the poor prognosis of the tumor. However, no experimental evidence of this peculiar venous tropism has been documented by now. One hypothesis might be that hepatoid cells are more proximal to the totipotent cells, such as fetal cells, from an ontogenetic standpoint, or else that cells of the colonic mucosa might possess liver specific genes normally in the repressed state, but they may be activated during the process of carcinogenesis, expressing cells with a hepatic phenotype. These assumptions need to be proven, and none of the hypotheses proposed about the origin and the biology of these tumors is convincing.

To the best of our knowledge, no case of hepatocellular carcinoma of colon-rectum has been treated by standard multichemotherapy used in an adjuvant and metastatic setting. Due to the evident lack of data about the treatment of this very rare entity, and given the absence of any approved regimen for hepatocellular carcinoma in adjuvant setting, we treated it as a carcinoma, administrating FOLFOX-4 regimen as adjuvant chemotherapy. The patient relapsed shortly after starting treatment. It is important to note that the disease had not spread to the liver, which is considered a common site of metastasis of this tumor, often rendering difficult the differential diagnosis with an hepatocellular carcinoma when metastasis are metachronous. Thereafter she was switched to FOLFIRI plus Bevacizumab as first-line treatment for metastatic disease, but she progressed after only 2 months of chemotherapy and she died 1 month later. This chemoresistance emphasizes even more how this cancer has an aggressive biological behavior with a very poor prognosis. Although one case is not enough to draw conclusions, it might be argued that hepatoid carcinoma of the colon is not sensitive to chemotherapy agents mostly used in colon cancer, sharing this behavior with the primary liver tumor counterpart. This raises the question of whether to treat it as a cancer of the colon or rather a cancer of the liver from the onset. However, in a recently reported case of hepatoid adenocarcinoma originating in the peritoneal cavity, Metzgeroth et al. [5] administered Sorafenib (Nexavar®), the only FDA-approved drug for advanced hepatocellular carcinoma. Despite temporary clinical improvement, the patient died 6 months after the diagnosis.

In conclusion, hepatoid adenocarcinoma is a rare variant of colon cancer associated with a poor prognosis despite an aggressive and multimodal strategy. Thus far, none of the hypothesis proposed about the origin and biology of these tumors is convincing, and no data about effective chemotherapy is available. The lack of any clinical benefit from the treatment we chose, causes us to question what we need to target in our treatment of patients with this rare disease.

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