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Original contribution

Molecular and cytogenomic profiling of hepatic adenocarcinoma expressing inhibinA, a mimicker of neuroendocrine tumors: proposal to reclassify as "cholangioblastic variant of intrahepatic cholangiocarcinoma"☆

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Summary Only a single case report exists in the literature of hepatic adenocarcinoma expressing InhibinA in a young woman, in which the authors proposed it to be a rare variant of intrahepatic cholangiocarcinoma (iCCA). We present novel molecular and histologic findings in our series of three cases occurring in young women and show these tumors may mimic well-differentiated neuroendocrine tumors (NET). Immunohistochemical (IHC) profiling was performed along with a next-generation sequencing (NGS) 47-gene solid tumor panel, and cytogenomic profiling via single-nucleotide polypmorphism microarray. IHC for inhibinA, chromogranin A (ChrA), and synaptophysin (Syn) was surveyed in liver tumors and in fetal liver. Two of the three patients recurred with metastatic disease with two confirmed deaths. Histological patterns present in the tumors included solid, trabecular, organoid, microcystic, and blastemal-like. IHC was positive for cytokeratin 7 in 3/3, cytokeratin 19 in 3/3, inhibinA in 3/3, ChrA in 3/3, Syn in 3/3, Sox9 in 2/3 and HepPar1 in 0/3. NGS was negative for pathogenic mutations. Recurrent cytogenomic abnormalities included gain of 17q, and loss of 6q. InhibinA was strong and diffusely expressed in 0/10 (0%) iCCA, 0/15 (0%) hepatocellular carcinomas (HCC), in the biliary component of 1/4 (25%) combined HCC-iCCA, 0/4 hepatoblastomas, 1/8 (13%) metastatic NET,

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and in 1/8 fetal liver tissues. We propose a classification of "cholangioblastic variant of intrahepatic cholangiocarcinoma" and molecular pathogenesis for this rare malignancy. Accurate identification on core biopsy is crucial for clinical management as it may mimic neuroendocrine neoplasms.

1. Introduction

Intrahepatic cholangiocarcinoma (iCCA) typically occurs in patients over the age of 65 in the United States with men being affected more often than women [1]. Risk factors include chronic liver disease and infections of the biliary tract [2-6]. Hepatic adenomas and hepatocellular carcinoma are typically included in the differential diagnosis when a relatively young woman without risk factors develops a large liver tumor. ICCA is exceedingly rare in this population.

In 2005, a single case of hepatic adenocarcinoma expressing inhibin in a 24-year-old woman was reported as an unusual variant of iCCA [7]. In this case, the tumor demonstrated strong biliary cytokeratin expression and diverse histological growth patterns including trabecular and pseudoglandular growth patterns with other areas demonstrating microcystic, organoid and tubular patterns. The tumor strongly expressed inhibinA.

Here we report 3 cases of hepatic adenocarcinoma expressing inhibinA occurring in relatively young women with clinical, immunophenotypic, and molecular genetic characterization. Each was diagnosed as a neuroendocrine neoplasm on biopsy with subsequent surgical resection revealing hepatic adenocarcinoma expressing inhibinA. Furthermore, we propose that hepatic adenocarcinoma expressing inhibinA should be reclassified and suggest a clinical algorithm to facilitate diagnosis.

2. Case presentations

2.1. Patient 1

2.1.1. Clinical presentation, imaging and laboratory workup, and preoperative management

A 17-year-old female presents with right-sided abdominal distension due to a right lobe liver mass found on abdominal computed tomography (CT) scan. Liver biochemical tests were within normal limits except for alkaline phosphatase, which was elevated at 138 U/L (reference range 32–91). Tumor markers including α-fetoprotein were within normal limits. She underwent a biopsy, which returned the diagnosis of malignant epithelial neoplasm with features of a neuroendocrine neoplasm. The patient received neoadjuvant chemotherapy and demonstrated clinical and partial radiologic response (Table 1).

2.1.2. Pathological evaluation

On pathological examination of the resection specimen, the tumor measured 23 × 12 ×8 cm. Histologically (Fig. 1), the tumor was composed of cuboidal cells with round nuclei in a variety of architectural growth patterns including trabecular, microcystic, pseudoglandular, and solid/hepatoid. No bile production was seen. Areas of dense cellularity with tubules in varying stages of apparent maturation resembling blastemal-like arrangements were noted (Fig. 1 B and C). There was no relationship between the blastemal-like areas and expression of any immunomarkers. Immunophenotying (Table 2) failed to demonstrate any hepatocellular differentiation (see Table 2). Biliary differentiation was confirmed by expression of cytokeratin 7, cytokeratin 19, and Sox9 (Table 2). Chromogranin A and synaptophysin staining was present throughout the tumor (Fig. 2). InhibinA staining was strong and diffusely positive (Fig. 2). Background liver was unrevealing of any chronic liver or biliary disease.

2.1.3. Postoperative management and outcome

Postoperatively, the patient was expectantly managed and received chemotherapeutic regimens (see Table 1). Surveillance revealed right-sided lung nodules with pathologic confirmation of metastatic recurrence at 38 months status post-resection. The patient died of disease at 41 months status post-resection (44 months overall survival).

2.2. Patient 2

2.2.1. Clinical presentation, imaging and laboratory workup, and preoperative management

A 44-year-old female presented with a history of abdominal distention with a CT scan of the abdomen identifying masses within the left lobe and right lobe of the liver. Past medical history was significant for paraganglioma status post resection and radiation 15 years prior to presentation and medroxyprogesterone acetate injections for contraception discontinued greater than 2 years prior to presentation. Liver biochemical tests revealed elevated alkaline phosphatase 219 U/L (38–126), AST 170 U/L (15–41), and ALT 146 U/L (14–54). Bilirubin was normal. A serum chromogranin A level was mildly elevated at 24 ng/mL (1.9–15.0 ng/mL). Plasma and urine vanillymandelic acid, catecholamines, and metanephrines were within normal limits. The clinical impression was that of recurrent paraganglioma.

2.2.2. Pathological evaluation

A biopsy of the mass was diagnosed as intermediate-grade neuroendocrine tumor (NET) with initial immunophenotyping showing expression of AE1/3, glypican-3, chromogranin A and synaptophysin with focal positivity for CK7 and CDX2. The patient underwent a surgical resection with negative margins. Histologically, the tumor was composed of a trabecular and solid/hepatoid growth pattern (Fig. 1). Immunophenotying (Table 2) failed to demonstrate any hepatocellular differentiation. Biliary differentiation was confirmed by strong and diffuse