Human Pathology (2016) **55**, 101–107

ELSEVIER

Human PATHOLOGY

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Original contribution

Hepatocyte differentiation markers in adenocarcinoma of the prostate: hepatocyte paraffin 1 but not arginase-1 is specifically expressed in a subset of prostatic adenocarcinoma ☆

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Received 23 February 2016; revised 4 April 2016; accepted 22 April 2016

Keywords:
HepPar 1;
Arginase-1;
Hepatoid;
Prostate;
Adenocarcinoma;
HCC

Summary Prostate adenocarcinoma and hepatocellular carcinoma (HCC) are common cancer types. Both may present with bone metastases, and both are known to be CK7/CK20 negative. Thus, diagnosis of less well-differentiated tumors at metastatic sites essentially relies on immunohistochemical confirmation. However, insufficient data exist on the expression status of the main 2 hepatocyte markers hepatocyte paraffin 1 (HepPar-1) and arginase-1 (Arg-1) in prostatic adenocarcinoma. We screened 557 prostate carcinoma cases for expression of these 2 markers using tissue microarrays. Sixty-four of 557 (11.5%) cases showed highly variable expression of HepPar-1 in 1% to 75% of tumor cells with a characteristically strong granular "mitochondrial" pattern. Only 13 cases (2.3%) expressed HepPar-1 in greater than 10% of the tumor cells. No correlation was seen with Gleason grade. On the other hand, 19 (3.4%) of 557 cases showed variable nonspecific cytoplasmic expression of Arg-1 distinct from the specific combined nucleocytoplasmic staining seen in normal liver and in HCC. Specifically, this Arg-1 pattern was seen only using one antibody lot and not another suggesting cross-reactivity. Only a single case showed specific nucleocytoplasmic expression of Arg-1 in the tumor cells. In conclusion, specific granular cytoplasmic staining for HepPar-1 is frequent in prostatic adenocarcinomas (11.5%) but usually focal and limited to less than 5% of tumor cells. This should not be misinterpreted as evidence of HCC, particularly in solid-pattern neoplasms. On the other hand, specific Arg-1 expression is very rare (0.18%), highlighting the value of Arg-1 in distinguishing HepPar-1–positive prostatic carcinoma from HCC at metastatic sites or in cases of liver metastasis from prostate carcinoma.

1. Introduction

Adenocarcinoma of the prostate and hepatocellular carcinoma (HCC) are prevalent cancer types with increasing frequency worldwide [1,2]. Although histologic diagnosis of

☆ Disclosures: The authors have no conflicts of interest or funding to disclose. This study was supported in part by the Johannes und Frieda Marohn-Stiftung of the Friedrich-Alexander University Erlangen-Nuremberg.
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http://dx.doi.org/10.1016/j.humpath.2016.04.016
0046-8177/

the primary tumor of both entities is usually straightforward in the appropriate clinical setting, the 2 entities on occasion pose great differential diagnostic confusion at metastatic sites. In particular, both HCC and prostatic adenocarcinoma frequently present as bone metastases, and both are essentially negative with specific cytokeratins used in the workup of metastatic adenocarcinomas, in particular CK7 and CK20. Furthermore, prostatic carcinoma can give rise to liver metastasis and on occasion may closely simulate the pseudoacinar pattern of HCC. Based on these joint features, differentiating prostate cancer metastasis from metastatic HCC can be challenging, in particular if the tumor presented with solid or trabecular growth pattern and other helpful clinical features are lacking. These observations underline the role of immunophenotyping as a highly useful adjunct tool in determining the origin of metastatic tumors. It is well known that a variety of adenocarcinomas from different sites, including in particular those arising in the gastrointestinal tract, may display hepatoid differentiation, histologically, by immunohistochemistry, or both, thus closely mimicking metastatic or primary HCC [3].

To date, a variety of markers have proven highly sensitive and relatively specific for HCC and for carcinomas with hepatoid differentiation. Among these immunomarkers, hepatocyte paraffin 1 (HepPar-1) [4–7], arginase-1 (Arg-1) [8–10], α-fetoprotein (AFP) [10], glypican-3 [11], and SALL4 [12,13] have been extensively studied, but data on expression of these markers in prostate cancer are very limited. Facing a consult case of primary prostatic adenocarcinoma showing prominent expression of HepPar-1 in a predominant solid component lacking conventional prostatic carcinoma markers except for retained NKX3.1, we noticed the very sparse literature on HepPar-1 expression in prostatic adenocarcinoma. We therefore performed the current study to gain insight into the frequency and distribution of the 2 most commonly used markers of hepatoid differentiation, HepPar-1 and Arg-1, in a cohort of 557 cases of primary prostatic carcinomas.

2. Materials and methods

The original study cohort comprised 2 sets of tissue microarrays (TMAs) containing a total of 603 cases of primary prostatic carcinoma. Histopathologic evaluation of each tumor case was performed by an expert uropathologist (A. H.). From each tumor, up to 3 cores (diameter, 1.5 mm) sampling the highest and lowest Gleason pattern were brought onto a recipient multiblock. Hematoxylin and eosin–stained slides were used to confirm the presence of carcinoma in the TMA cores. Immunohistochemical studies were performed on 3-μm sections cut from paraffin blocks using a fully automated system ("Benchmark XT System"; Ventana Medical Systems, Tucson, AZ). Normal prostate and liver tissue was used as on-slide positive controls for prostatic and hepatocytic markers, respectively. Negative IHC control was obtained by omitting the primary antibody to rule out an artificial staining reaction caused by the staining kit itself. Biotin-free UltraView DAB Kit (Ventana Medical Systems) was used as immunodetection system, which includes H_2O_2 for blocking endogenous peroxidase activity.

HepPar-1 was obtained from Dako (HepPar-1, clone OCH1E5, 1:200 dilution; Dako, Glostrup, Denmark). For Arg-1, 2 different antibody lots were evaluated; both were obtained from Cell Marque (Arg-1, clone SP156, lot 1314909D and lot 1426205A, ready-to-use; Cell Marque, Rocklin, CA). The first lot of the Arg-1 (lot 1314909D) was used for staining the first TMA set containing 503 cases. The second (new) lot (lot 1426205A) was used to stain all of the cases on both TMA sets.

Assessment of the TMAs was based both on staining intensity (0, negative; 1, weak; 2, moderate; 3, strong) and extent (0, negative; 1, < 5% of cells; 2, 5%-10% of cells; 3, 11%-25% of cells; 4, 26%-50% of cells; and 5, > 50% of cells staining positive). For HepPar-1, only unequivocal granular cytoplasmic staining was considered specific. Regarding Arg-1, only combined nucleocytoplasmic staining similar to that seen in normal liver was considered specific. Any other aberrant staining was recorded as well. As a control group, we examined 60 HCCs on TMAs for expression of the prostate markers PSA (prostate-specific antigen, clone ER-PR8, 1:200; Zytomed, Berlin, Germany), prostein (clone 10E3, 1:50; Dako), PSP (prostate secretory protein, clone PASE/4LJ, 1:50; Zytomed), and NKX3.1 (polyclonal, 1:50; Biocare Medical, Concord, CA). This study has been performed in accordance with accepted principles of ethical and professional conduct for biomedical scientific research and is covered by ethical vota of the medical faculty of the Friedrich-Alexander University of Erlangen-Nuremberg for retrospective translational research activities.

3. Results

3.1. Index case

Representative images of the index case (transurethral resection) are shown in Fig. 1. The tumor was composed of a minor conventional acinar component that expressed PSA, prostein, and NKX3.1 but lacked HepPar-1 and Arg-1. The more extensive tumor component showed loss of PSA and prostein but expressed NKX3.1 and strongly diffusely HepPar-1 with the characteristic coarse granular cytoplasmic (mitochondrial) pattern. Arg-1 was negative in this hepatoid component.

3.2. Staining pattern of HepPar-1 and Arg-1 on TMAs

Among the 603 cases contained in the TMAs, 46 cases were excluded either due to drop-off of the cores on the immunostained slides or because only normal tissue was seen in the hematoxylin and eosin–stained sections used for immunohistochemistry. Thus, a total of 557 cases had assessable results, and they represent the cohort of this study. Overall, variable