Oncology

Prostatic Adenocarcinoma With Hormone Exposure Related Changes in a Patient With Hepatic Cirrhosis – Value of Autopsy in a Case Report

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ABSTRACT

Hepatic cirrhosis is commonly associated with hyperestrogenism. Previous studies have reported morphologic changes in benign and malignant prostate tissue exposed to estrogen or anti-androgens. To our knowledge, histopathologic features of prostatic adenocarcinoma in patients with cirrhosis have not been well-reported. We present a case of incidental, but pathologically significant, prostatic adenocarcinoma detected on autopsy in a 67-year-old male patient with cirrhosis and spider angiomata. The morphologic and immunohistochemical features (including variable ERG expression) of the prostatic adenocarcinoma were consistent with hormone exposure related changes, suggesting that cirrhosis-induced elevated estrogen-to-testosterone ratio and exogenous hormone therapy might induce similar phenotypes.

Introduction

Hepatic cirrhosis is known to be associated with hyperestrogenism; manifestations in males include testicular atrophy, gynecomastia, and decreased libido. Schenken et al described nuclear size reduction, loss of nucleoli, chromatin condensation, nuclear pyknosis, and cytoplasmic vacuolization in prostatic adenocarcinoma after estrogen treatment.1 Subsequent studies demonstrated these features as well as reduced mitotic activity in prostatic adenocarcinoma, in addition to squamous metaplasia and basal cell hyperplasia in background benign prostate glands.

Anti-androgen therapy has been reported to cause similar changes in prostatic adenocarcinoma, and the malignant prostate glands may be largely degenerated, leaving cleft-like spaces with irregular acid mucinous pools and rare carcinoma cells.2 Importantly, prostatic adenocarcinoma shows variable response to hormone exposure, both within a tumor and between tumors from different patients.

Barr and Sommers reviewed 100 autopsied cases of hepatic cirrhosis and found changes indicative of estrogen effect (squamous metaplasia and/or atrophy) more frequently in prostate tissues of patients with cirrhosis than in controls.3 The morphology of the identified cancers was not described. The degree of estrogenic effect seen in the prostates of the majority of cirrhotic patients was comparable to that seen with stilbestrol therapy for prostatic cancer.

This report provides the autopsy, clinicopathologic, immunohistochemical and fluorescence in situ hybridization (FISH) description of an incidental, but pathologically significant, prostatic adenocarcinoma identified in a fatal case of cirrhosis.

Case presentation

Our patient was a 67-year-old man with history of cirrhosis secondary to autoimmune hepatitis and one month of progressive...
Figure 1. Histologic features of benign and malignant prostate tissue at the time of autopsy in a patient with cirrhosis. (A) Benign prostate glands demonstrating a prominent basal cell layer (H&E, 100× with scale bar 200 microns). (B) Prostatic adenocarcinoma demonstrating small glands with atrophic features (H&E, 200× with scale bar 100 microns). (C) Prostatic adenocarcinoma with relatively small and pyknotic nuclei infiltrating around a residual benign prostatic gland (toward top of the image, H&E, 200× with scale bar 100 microns). (D) PIN4 immunohistochemistry demonstrates loss of basal cell marker expression in the prostatic adenocarcinoma with retained expression in the single benign gland toward top of the image (H&E, 200× with scale bar 100 microns). (E) Prostatic adenocarcinoma cells resembling histiocytes with small nuclei, indistinct nucleoli, and vacuolated cytoplasm (H&E, 400× with scale bar 50 microns). (F) Cleft-like spaces filled with mucin and rare carcinoma cells (H&E, 200× with scale bar 100 microns). (G-H) Prostatic adenocarcinoma adjacent to metastatic poorly differentiated hepatocellular carcinoma within a lymphovascular space (H&E, 100× with scale bar 200 microns, and H&E, 200× with scale bar 100 microns, respectively).
dyspnea, transferred to our hospital for liver transplant evaluation in the setting of possible hepatorenal syndrome. Chest CT showed ground-glass opacities concerning for infection, and broad-spectrum antibiotics including coverage for *Pneumocystis jiroveci* were started. His decline continued with development of refractory lactic acidosis and acute kidney injury, so he was transitioned to comfort care. He was pronounced dead five days after admission.

He had no known personal or family history of cancer. Antemortem work-up included serum alpha fetoprotein and prostate-specific antigen (PSA), which were within the reference ranges, as well as abdominal ultrasound which demonstrated cirrhosis with no definitive mass lesion. The autopsy revealed that the cause of death was complications of widely metastatic poorly differentiated hepatocellular carcinoma, including type B lactic acidosis. An incidental prostatic adenocarcinoma (1.5 cm) with invasion into periprostatic fat (pT3a) was also seen.

Microscopically, focal areas of the prostatic tumor showed both well- and poorly formed glands with cells demonstrating nucleomegaly characteristic of prostatic adenocarcinoma. The majority of the prostatic adenocarcinoma, however, demonstrated areas with atrophic features, mucinous pools with absent-to-rare carcinoma cells (reminiscent of acellular clefts), and tumor cells with vacuolated cytoplasm and small nuclei with inconspicuous nucleoli, resembling histiocytes (Fig. 1). The background benign prostatic tissue showed a prominent basal cell layer with foci of basal cell hyperplasia. Metastatic hepatocellular carcinoma was also identified within the lymphovascular spaces in the prostate gland (Fig. 1).

Immunohistochemical staining confirmed diffuse PSA and PSMA expression in the prostate cancer cells, which were as expected negative for basal cell marker (p63 and CK34BE12) expression. Focal AMACR and variable (absent to moderate nuclear) androgen receptor expression were present. ERG expression, which when positive in our series of untreated patients is diffusely strong,

There was no reported exogenous hormone intake or exposure, and hence, based on the clinical presentation of hepatic cirrhosis and associated hyperestrogenism-induced stigmata like spider angiomata, we attributed the morphological changes seen in this prostatic adenocarcinoma to cirrhosis-induced hormonal imbalance. By convention, this cancer was not assigned a Gleason score due to the hormone exposure related changes.

**Discussion**

It is well-established that hepatic cirrhosis is associated with an elevated estrogen-to-testosterone ratio linked to a spectrum of clinical stigmata. To our knowledge, histologic features of prostatic adenocarcinoma in patients with hepatic cirrhosis have not been well-reported.

Herein, we report the presence of a pathologically significant prostatic adenocarcinoma (stage pT3a) identified in a patient with cirrhosis and normal serum PSA. The majority of the prostatic adenocarcinoma demonstrated features that have been described in the context of exogenous estrogen or anti-androgen therapy, including (1) nuclear size reduction, inconspicuous nucleoli, and cytoplasmic vacuolization and (2) cleft-like spaces with mucinous

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**Figure 2.** Immunohistochemical and fluorescence in situ hybridization analysis of prostatic adenocarcinoma. (A) Tumor cells show diffuse moderate-to-strong PSA expression (200× with scale bar 100 microns), (B) variable AR expression (H&E, 200× with scale bar 100 microns), and (C) variable ERG expression (H&E, 200× with scale bar 100 microns). (D) The tumor was diffusely positive for ERG rearrangement by FISH at the genomic level. Dual-color, break apart FISH method to determine ERG rearrangement status: wild type ERG allele = yellow signal (colocalized signals), and rearranged ERG allele with loss of the 5′ ERG (red) probe = single green signal.
pools and sloughing carcinoma cells. Squamous metaplasia was not seen in the background benign prostatic glands; however, benign glands demonstrated basal cell hyperplasia, which is sometimes associated with estrogen exposure.

TMPRSS2-ERG is an ETS gene fusion specific to neoplastic prostate that occurs in more than 40% of localized and metastatic prostate cancers in PSA-screened Caucasian cohorts. ERG immunohistochemistry is less sensitive for detection of ERG rearrangements in tumors that have been treated with hormone therapy than in untreated tumors, presumably due to dysregulation of androgen receptor signaling. This patient’s prostatic adenocarcinoma demonstrated an ERG rearrangement at the genomic level and variable (absent to strong) ERG protein expression, akin to what has been previously documented in patients with therapy-related changes.

Although this patient did not receive exogenous hormone therapy, the histologic and immunohistochemical characteristics of his prostate cancer are similar to those seen with estrogen or anti-androgen therapy. Because there was no known indication for testing, the patient’s sex hormone levels are unknown. Spider angiomata, which are known stigmata of cirrhosis-induced hormonal imbalance, were present on his face and chest. Overall, these findings indicate that the phenotypic features seen within this patient’s prostatic adenocarcinoma are related to his underlying cirrhosis-associated hormonal imbalance.

The possibility of development of prostatic adenocarcinoma with hormone exposure related changes in a patient with cirrhosis has important implications for understanding prostate cancer tumorigenesis in these patients, and can be a challenge in the diagnostic needle biopsy setting, particularly for initial diagnosis. Due to the high incidence of prostate cancer, it is important to recognize that hormone exposure related changes may be seen within prostatic adenocarcinoma in cirrhotic patients.

Conflict of interest
No conflict of interest.

References

1. Schenken JR, Burns EL, Kahle PJ. The effect of diethylstilbestrol dipropionate on carcinoma of the prostate gland. II. Cytologic changes following treatment. J Urol. 1942;48:99—112.
2. Petraki CD, Sifkas CP. Histopathological changes induced by therapies in the benign prostate and prostate adenocarcinoma. Histol Histopathol. 2007;22:107—118.
3. Barr RW, Sommers SC. Endocrine abnormalities accompanying hepatic cirrhosis and hepatoma. J Clin Endocr Metab. 1957;17:1017—1025.
4. Udager AM, Shi Y, Tomlins SA, et al. Frequent discordance between ERG gene rearrangement and ERG protein expression in a rapid autopsy cohort of patients with lethal, metastatic, castration-resistant prostate cancer. Prostate. 2014;74:1199—1208.
5. Mehra R, Tomlins SA, Yu J, et al. Characterization of TMPRSS2-ETS gene aberrations in androgen-independent metastatic prostate cancer. Cancer Res. 2008;68(10):3584—3590.