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Differentiating intraductal carcinoma of the prostate from high-grade prostatic intraepithelial neoplasia: Why it matters

ABSTRACT

Differential diagnosis between intraductal carcinoma of the prostate (IDC-P) and high grade prostatic intraepithelial neoplasm (HGPIN) may show similar morphology and present diagnostic challenges. However, the clinical consequences following each diagnosis are distinct. While IDC-P is most likely associated with high grade invasive carcinoma, HGPIN is a precancerous lesion that is often an isolated finding without accompanying invasive cancer. IDC-P is characterized by solid or dense cribriform architecture with enlarged glands, significant nuclear pleomorphism with markedly enlarged nuclei up to 6 times larger than normal acinar epithelial cells, frequent mitotic figures and frequent comedonecrosis. HGPIN shows cytologic atypia with hyperchromatic nuclei, up to 2-3 times larger nuclei than non-neoplastic epithelium and prominent nucleoli. If a definitive diagnosis cannot be rendered due to overlapping morphologic features, especially in limited biopsy specimens, the borderline status should be reported to recommend a close follow-up.

CLINICAL SIGNIFICANCE OF IDC-P VERSUS HGPIN

Intraductal carcinoma of the prostate (IDC-P) and high-grade prostatic intraepithelial neoplasia (HGPIN) are pathogenetically and prognostically distinct entities which although sharing some overlapping morphologic features are associated with very different clinical implications. This review highlights the diagnostic and prognostic distinction between HGPIN and IDCP.

HGPIN is a non-obligate precursor lesion of invasive cancer whilst IDC-P is a high-grade malignant lesion likely representing intraductal spread of high grade invasive cancer. IDC-P is typically accompanied by high-grade invasive carcinoma on needle core biopsy, and in radical prostatectomies usually is associated with invasive cancer showing poor prognostic findings such as high Gleason score (>7), large tumor volume, extraprostatic extension (EPE) and positive margins [1]. Rarely on needle core biopsy may IDC-P be an isolated finding without evidence of concurrent invasive carcinoma. However, most of these cases are subsequently shown to coexist with invasive high grade carcinoma on subsequent RP. Thus the identification on biopsy of IDC-P without or without an invasive component warrants definitive treatment [2].

In contrast, HGPIN is often seen in biopsies with no invasive carcinoma [3,4], and the presence of focal HGPIN on needle biopsy is not associated with an increased cancer risk on subsequent biopsy at least on short term follow-up. Extensive HGPIN (involving more than 2 cores), however, warrants closer follow-up and rebiopsy sooner due to an increased risk of prostate cancer on repeat biopsy comparable to an ASAP (atypical small acinar proliferation) diagnosis although less than IDC-P [5]. It is very import therefore to differentiate between IDC-P and HGPIN, particularly on needle biopsies, since distinction of these will results in very different clinical managements.

The diagnosis of IDC-P is morphologic based and if extensive is usually straightforward. Morphologic distinction between IDC-P and HGPIN is not always clear cut however and there are cases that show features bridging these two.

PATHOLOGIC FEATURES OF IDC-P AND HGPIN

While there is no formal diagnostic criteria, IDC-P is characterized by solid or dense cribriform architecture, significant nuclear pleomorphism with markedly enlarged nuclei up to 6 times larger than nor-

mal acinar epithelial cells, frequent mitotic figures and frequent comedonecrosis [2,6]. By definition, ducts involved by IDC-P possess a preserved basal cell layer demonstratrable by immunohistochemical stains such as high molecular weight cytokeratin (HMWCK) or p63. Other helpful features to support a diagnosis of IDC-P include preserved duct/lobular architecture, increased duct/gland size that are at least 2 times the normal size, and the presence of central lumen-spanning proliferation separated from the stroma [4,6].

HGPIN has several different architectures including tufting, micropapillary, flat and cribriform pattern [7]. Although the most important diagnostic features of HGPIN is cytologic atypia with hyperchromatic nuclei2-3 times larger nuclei than nonneoplastic epithelium and prominent nucleoli, the cellular atypia is not as pronounced as typically seen in IDC-P. Although diagnostic confusion may arise with cribriform HGPIN, HGPIN lacks the solid or dense cribriform patterns seen in IDC-P with much less cellularity in the glandular lumen. Comedonecrosis is almost never found in HGPIN [2].

Problematic cases are usually characterized by small, architecturally simple HGPIN glands lined by nuclei with significant pleomorphism beyond what would be normally seen, or where dense cribriform proliferations of atypical cells are seen in small glands or incompletely represented large ducts. The prognosis of these cases is currently unknown. If diagnostic uncertainty is present and a definitive diagnosis cannot be rendered between IDC-P and HGPIN, the borderline status of the case should be reported by pathologist to clinician and repeat biopsy should be strongly recommended for further assessment [2,8].

OTHER ENTITIES IN DIFFERENTIAL DIAGNOSIS

Other important differential diagnoses include cribriform acinar adenocarcinoma, ductal adenocarcinoma, and intraductal spread of urothelial carcinoma [2]. High grade cribriform prostatic adenocarcinoma may mimic characteristic architectures of IDC-P with dense cribriform morphology and comedonecrosis. Irregular infiltrating borders that lack basal cells should indicate cribriform cancer as opposed to smooth and round borders of IDC-P. Irregular infiltrating borders of invasive carcinoma do not fit to the normal duct contours or branching patterns of prostatic ducts. Basal cell stains such as HMWCK and/or p63 can be particularly helpful in needle core biopsy specimens.

Ductal adenocarcinoma of the prostate should also be considered in differential diagnosis of IDC-P when cribriform pattern of atypical glands are present. Ductal adenocarcinoma, however, is characterized by large slit-like space in cribriform glands, tall columnar cells, fibrovascular cores, and usually absent basal cell layer. Cribriform glands of IDC-P show small rounded lumen, cuboidal cells without fibrovascular cores. Differential diagnosis between IDC-P versus high grade cancer or ductal adenocarcinoma has somewhat less clinical consequences as all 3 entities should be treated in a similar fashion and represent bad prognosis.

Occasionally, intraductal spread of urothelial carcinoma may be in differential diagnosis. Intraductal spread of urothelial carcinoma is rarely associated with glandular features or cribriform pattern, but solid nests of highly atypical nuclei seen in the presence of surrounding basal cell layer can mimic IDC-P. Immunohistochemical study can be very helpful in this setting since urothelial carcinoma is usually positive for HMWCK, thrombomodulin and GATA3 while IDC-P is negative for these markers and positive for PSA, PSMA, P501S, and NKX3.1 [9,10].

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