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Immunohistochemical pitfalls in prostate pathology

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Summary The diagnosis of prostatic adenocarcinoma relies on a constellation of architectural, cytological, and immunohistochemical features. Although the diagnosis of prostatic adenocarcinoma is straightforward in most cases, due to earlier detection of the disease in the modern era, pathologists have become increasingly challenged in diagnosing small foci of cancer when only a few atypical glands are present in needle biopsies. Immunohistochemistry has therefore become an essential tool in the evaluation of such foci to confirm the absence of basal cells. In this context, the 2 most commonly used basal cell markers are anti-keratin 34BE12 and p63. Furthermore, α-methylacyl-CoA racemase, a marker found to be overexpressed in the cytoplasm of prostatic adenocarcinoma glands, is also commonly used in routine practice. Another diagnostic role of immunohistochemistry is to confirm the prostatic origin of the tumor in the primary or metastatic setting of high-grade prostatic adenocarcinoma, which may be confused with nonprostatic carcinomas. We herein review the utility as well as the limitations of immunohistochemistry in the diagnosis of prostatic adenocarcinoma, and we describe the most important pitfalls in the interpretation of various immunostains that pathologists should be aware of to minimize misdiagnoses.

1. AMACR immunostaining: utility and pitfalls

α-Methylacyl-CoA racemase (AMACR) is an enzyme involved in β-oxidation of branched-chain fatty acids, and it is significantly up-regulated in prostatic adenocarcinoma. Antibodies have been developed against its gene product, P504S [1,2]. AMACR is highly sensitive for prostatic adenocarcinoma, with sensitivities ranging from 82% to 100% without significant variation between different Gleason grades [3-5]. This sensitivity appears to be similar when using polyclonal or monoclonal P504S antibodies [6]. AMACR positivity in carcinoma is characterized by intense cytoplasmic reactivity with granular quality, sometimes localized to the apical surface. In benign glands, AMACR staining is negative or weakly positive; therefore, AMACR overexpression is best evaluated by comparing its staining intensity between malignant glands and the surrounding benign glands. The main utility of AMACR is in the diagnosis of small foci of carcinoma in needle biopsies. As negative staining for basal cell markers is not necessarily diagnostic of carcinoma, AMACR positivity can increase the level of confidence in establishing a definitive malignant diagnosis [7,8]. This being said, there are several caveats that should be taken in consideration when assessing AMACR

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staining: AMACR is as frequently overexpressed in high-grade prostatic intraepithelial neoplasia (HGPIN) as in adenocarcinoma (Fig. 1A,B). Therefore, in the context of a small number of glands totally negative for basal cells where HGPIN is a consideration histologically, positivity of those glands for AMACR should not be construed as a definitive evidence of adenocarcinoma. Also, some conflicting studies have shown relative decrease in AMACR immunoreactivity

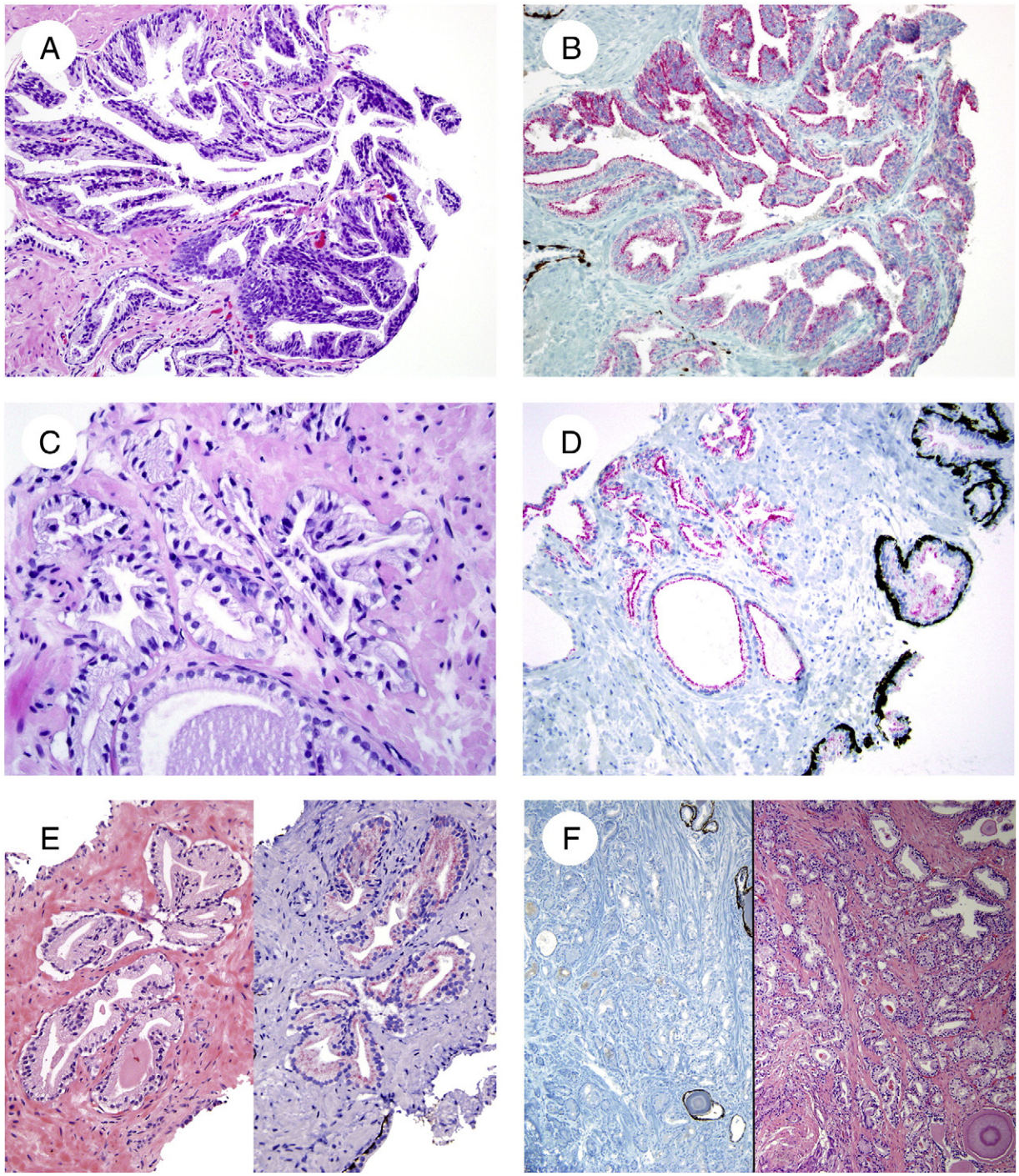

Fig. 1 A, HGPIN on needle biopsy. B, Same case as A: positive AMACR staining (red chromogen) with an absence of basal cells (brown chromogen). Despite this staining pattern, the H&E morphology is typical of HGPIN. The main differential diagnosis in this case is with HGPIN-like ductal adenocarcinoma. However PIN-like ductal adenocarcinoma consists of glands with predominantly a flat lining and lacks branching glands. C, Partial atrophy. D, Same case as C: positive AMACR staining (red chromogen) with an absence of basal cells (brown chromogen). E, Benign glands on H&E (left) with immunohistochemistry (right) showing a lack of basal cells (brown chromogen) and positive AMACR (red chromogen). F, Adenocarcinoma (right). Triple cocktail stain (left) where tumor shows lack of basal cells (note few benign glands with positive p63 and HMWCK). The tumor is negative for AMACR (lacks red cytoplasmic positivity).