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Original article

Focal positive prostate-specific membrane antigen (PSMA) expression in ganglionic tissues associated with prostate neurovascular bundle: Implications for novel intraoperative PSMA-based fluorescent imaging techniques☆

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Abstract

Objective: Prostate specific membrane antigen (PSMA) is primarily expressed in glandular prostatic tissue and is frequently utilized to detect primary or metastatic prostatic adenocarcinoma (CaP). A purported novel application of PSMA detection is the intraoperative real-time identification of CaP using radioimmunoscintigraphy to define the extension of the surgical resection. Considering that PSMA expression has been reported in other tissues, we evaluated its immunoexpression in prostatic neurovascular bundle elements to assess the convenience and safety of the aforementioned procedure.

Materials and methods: Twenty consecutive specimens of radical prostatectomy (RP) were retrieved from our surgical pathology archives. PSMA immunoexpression (Clone 3E6, DAKO) was assessed in a representative section from each specimen containing neurovascular bundle elements.

Results: PSMA expression was documented in 20/20 of examined CaP slides. Most cases exhibited an apical/cytoplasmic or cytoplasmic with membranous accentuation pattern of staining. Focal weak to moderate cytoplasmic staining was detected in associated ganglionic tissue in 3/15 of the examined RP. In all cases, staining was cytoplasmic, less extensive, and weaker than the pattern observed in CaP. None of the peripheral nerve sheath cells or lymphovascular components of the examined neurovascular bundles were positive for PSMA.

Conclusions: We found focal positive PSMA expression in the ganglionic cells of the prostatic neurovascular bundle. Our results suggest that the radioimmunoscintigraphic detection of radiolabeled PSMA antibodies might not be entirely specific for prostatic cells; this observation must be taken into account should an intraoperative PSMA-based fluorescent imaging technique be used to define the extension of the surgical procedure.

Keywords: Prostate specific membrane antigen (PSMA); Prostate carcinoma; Radioimmunoscintigraphy; Radiolabeled antibodies; Fluorescent imaging technique; Radical prostatectomy

1. Introduction

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein that is primarily expressed in glandular prostate tissue. Besides its application in the differential diagnosis of purported prostatic tumors using tumor tissue samples, PSMA is frequently utilized to detect prostatic adenocarcinoma (CaP) recurrences or metastasis to lymph nodes, soft tissues, or bone using radioimmunoscin-

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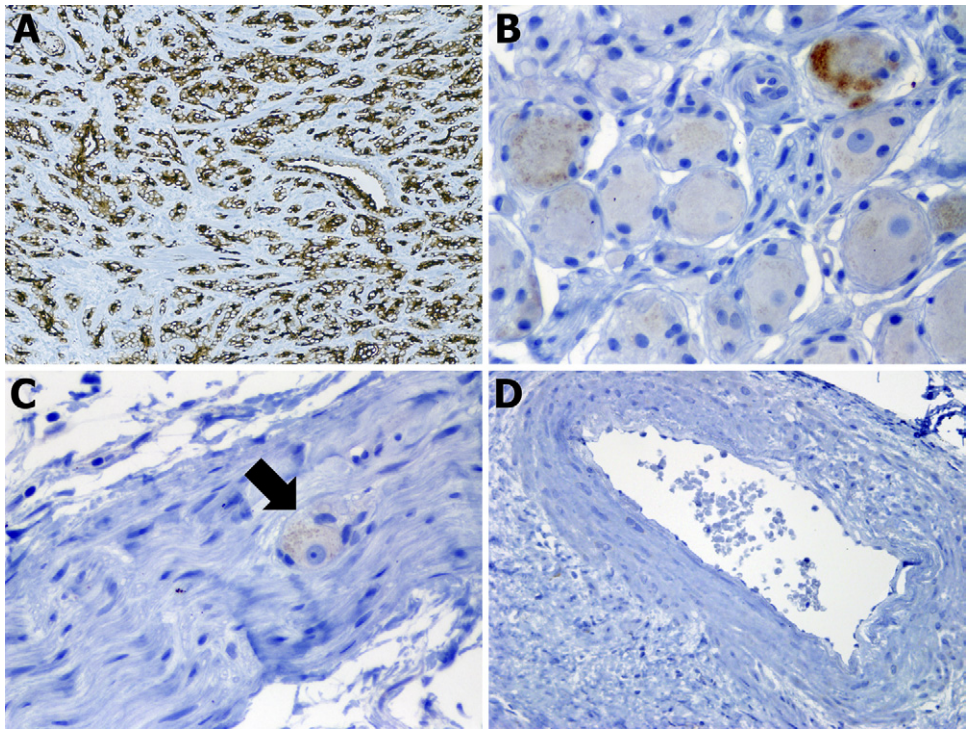

Fig. 1. Patterns of PSMA expression. (A) Prostatic adenocarcinoma, Gleason score 3+4=7, with strong and diffuse PSMA immunoexpression in tumor cells. (B) Ganglionic cells showing focal, weak cytoplasmic PSMA expression. (C) Peripheral nerve sheath cells negative for PSMA expression; note the ganglionic cell (arrow) with weak cytoplasmic PSMA positivity. (D) Vascular element negative for PSMA expression. (Color version of figure is available online.)

tigraphic detection of radiolabeled PSMA antibodies [1–4]; in addition, considering the putative advantages of a PSMA-targeted therapy in hormone-resistant and disseminated CaP [2,5–9], there is a strong interest in defining the tissue lineage specificity of PSMA expression. A real time intraoperative imaging technique using a newly developed low molecular weight urea-based compound that binds to PSMA and fluoresces in the NIR spectrum is being pursued at our institution. Such intraoperative techniques could help decrease the rate of positive surgical margins at radical prostatectomy (RP). In the current study, we evaluated PSMA expression in neurovascular bundle elements including peripheral nerve, ganglion, and lymphovascular tissue in order to assess the feasibility of the above intraoperative technology.

2. Materials and methods

Twenty consecutive RP specimens were retrieved from our surgical pathology archives. PSMA immunoexpression was assessed in a representative section from each specimen containing neurovascular bundle elements using a PSMA monoclonal antibody (Clone 3E6, DAKO, Carpinteria, CA). PSMA expression was evaluated by 2 pathologists. An intensity (1: weak; 2: moderate; 3: strong) and extent (1: <25%; 2: 25%–75%; 3: >75%) score was assigned in each RP for available CaP, neurovascular bundle elements, and associated ganglion tissue.

3. Results

As expected, PSMA expression was documented in 100% (20/20) of examined CaP tumors. Most cases exhibited an apical/cytoplasmic or cytoplasmic with membranous accentuation pattern of staining (Fig. 1A). Focal weak to moderate cytoplasmic staining was detected in associated ganglionic tissue in 3/15 (20%) of the examined RP (Fig. 1B). In all cases, staining was cytoplasmic, less extensive, and weaker than the pattern observed in CaP. None of the peripheral nerve sheath cells or lymphovascular components of the examined neurovascular bundles were positive for PSMA (1C and D). Data is summarized in Table 1.

4. Discussion

PSMA, a type II transmembrane protein with folate hydrolase and neuropeptidase functions, has a high specificity for benign and malignant prostatic tissue [4]. The reported immunohistochemical positivity of PSMA in CaP ranges from 57% to 100% [6,10] with most positive cases showing strong cytoplasmic staining. Various patterns of PSMA immunoexpression have been described, including apical, apical/cytoplasmic, cytoplasmic with membranous accentuation, and cytoplasmic only. The first 3 patterns of staining are more specific for CaP [4]. In addition, the vast majority of metastatic CaP maintain strong PSMA immunoexpression [4,6]. However, despite some early claims, PSMA