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CASE REPORT

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Incidental detection of localized prostate cancer with low PSA by computed tomography scan: A report of two cases

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Abstract

Serum prostate-specific antigen (PSA) levels play an important role in the screening and diagnosis of prostate cancer (PCa). The recommended PSA cut-off in PCa screening is 4 ng/ml. We report two cases of localized PCa with low PSA levels that were incidentally found by computed tomography (CT) performed for another disease.

KEYWORDS

low prostate-specific antigen, neuroendocrine, prostate cancer, prostate cancercase report

1 | INTRODUCTION

Prostate-specific antigen (PSA) is a glycoprotein secreted by the epithelial cells of the prostate and neoplastic prostate tissue. It belongs to the kallikrein peptidase family. PSA was first discovered in seminal plasma by Hara et al.[1] Serum PSA is useful as a screening test for PCa and as a tumor marker for monitoring the response to therapy.[2] It is generally accepted that PCa is unlikely if a patient's PSA level is between 0 and 2.5 ng/ml. The recommended PSA cut-off value for PCa screening is 4 ng/ml. In one study involving 113 patients with PCa, PSA levels were elevated in 93% of the patients, resulting in a specificity of 55%.[3] However, clinically significant PCa can be diagnosed in patients with a serum PSA value of <4 ng/ml. The majority of sporadic cases of low PSA PCas are metastatic tumors.[4–6] Here we present two cases of localized clinically significant PCa with PSA levels <3 ng/ml diagnosed incidentally by computed tomography (CT).

2 | CASE PRESENTATION

2.1 | Case 1

A 61-year-old man underwent CT for a pancreatic cyst that was incidentally detected on abdominal ultrasound. A contrast-enhanced lesion was detected in the right lobe of the prostate (Figure 1A,B) and he was referred to our department for further evaluation. He did not have a family history of PCa and his medical history included appendectomy and bronchial asthma (without medication for 19 years). The patient did not exibit any urinary tract symptoms. Digital rectal examination (DRE) revealed a hard nodule in the right lobe of the prostate. The PSA level was 2.54 ng/ml, and the free-total PSA ratio was 9.6%. T2-weighted magnetic resonance imaging (MRI) taken with Toshiba Excelart Vantage MRT-2003 (1.5T), body coil Atlas Speeder MJAB-157A, and spine coil Atlas Speeder MJAS-147A demonstrated a

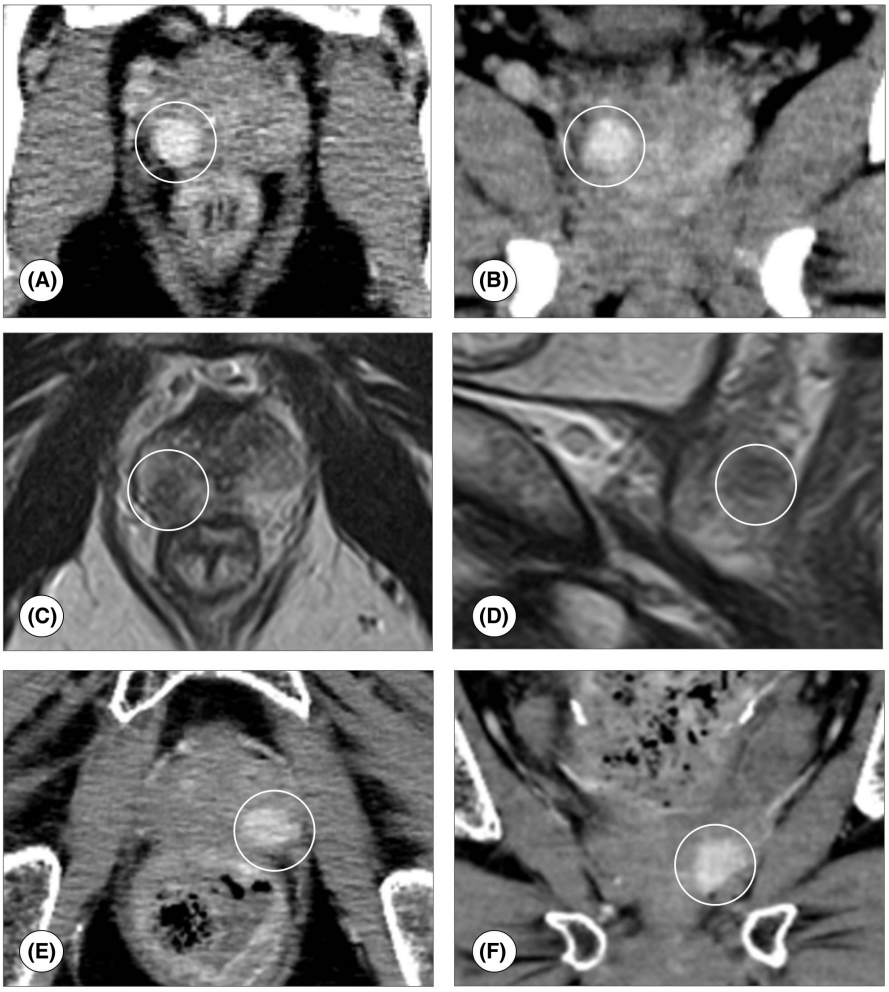

FIGURE 1 Computed tomography scans and magnetic resonance images. In case 1, computed tomography revealed a contrast-enhanced nodule in the right lobe of the prostate (axial [A] and coronal [B] view). The nodule was hypointense on T2-weighted magnetic resonance images (axial [C] and sagittal [D] view). In case 2, computed tomography revealed a contrast-enhanced nodule in the left lobe of the prostate (axial [E] and coronal [F] view)

hyperintense nodule (1.1 × 9.0 × 8.0 mm), with a Prostate Imaging Reporting and Data System (PI-RADS) score of 4. Contrast-enhanced CT revealed a hyperenhancing mass (Figure 1C,D) 1.3 × 1.1 cm in the right peripheral zone. No lymph nodes or distant metastases were detected. The patient underwent trans-rectal ultrasound (TRUS)-guided transrectal prostate biopsy and the pathological examination revealed an adenocarcinoma Gleason score (GS) of 4 + 5 = 9 in the right lobe (5 positive cores out of 12 cores). Three months later, the patient underwent radical retropubic prostatectomy (RRP) with lymph node dissection (bilateral obturator and internal iliac nodes). Pathological examination confirmed the diagnosis of adenocarcinoma GS 4 + 5 = 9 in the right lobe of the prostate (Figure 2A). Surgical margins were negative and no extracapsular extention, seminal vesicles invasion or pelvic lymph node metastases were detected. The International Society of Urological Pathology (ISUP) grade was 5. No small-cell or large-cell cancer tissue components were present. Immunohistochemical staining was positive for PSA (Figure 2B) and synaptophysin (Figure 2C). Sporadic cells in the basal cell compartment with cell processes projecting into the layer of luminal cells were positive for chromogranin A (Figure 2D) resembling neuroendocrine (NE) cells in the normal prostate.[7] The neuron-specific enolase (NSE) staining was negative. The lymph nodes were negative for metastasis. TNM stages were pT2a, pN0, M0, R0, G 2–3 (according to WHO classification). The PSA was evaluated monthly and then the patient was evaluated at trimonthly outpatient visits with biochemical profile, PSA and contrast enchanced CT. The PSA levels decreased to 0 ng/ml 2 months postoperatively. Two and a half years postoperatively without any additional treatment PSA remained 0.0 ng/ml and no signs of recurrence or metastasis are observed on CT at that time point.

2.2 | Case 2

A 71-year-old man with a past history of dyslipidemia, alcohol-related liver disease, low anterior resection for rectal cancer, pubic bone fracture, and spinal disc herniation was admitted to our hospital with ileus, which was managed conservatively. A contrast-enhanced lesion (1.3 × 1.0 cm) in the far lateral posterior part of the left lobe of the prostate was detected on the CT scan (Figure 1E,F)

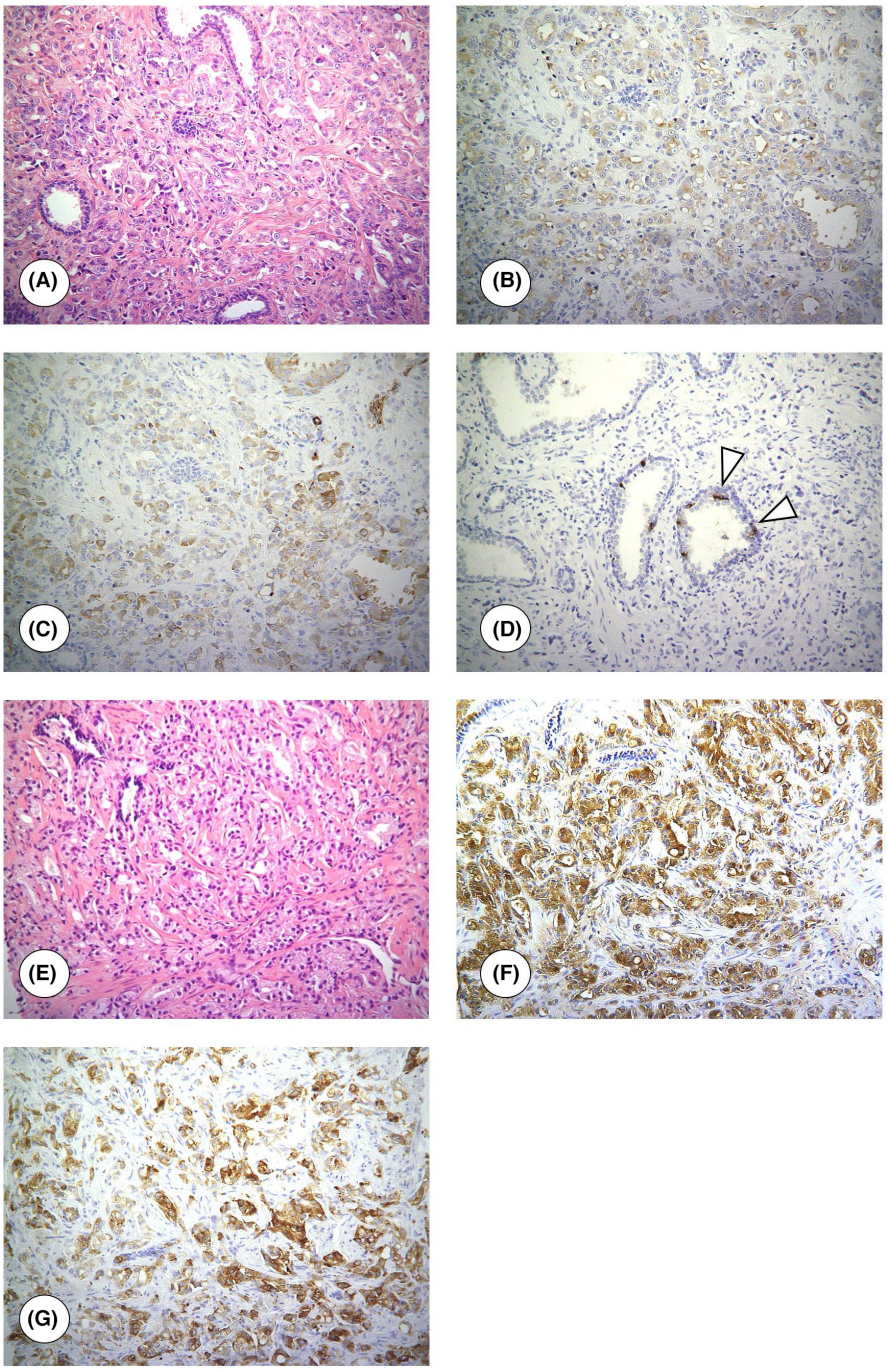

FIGURE 2 Radical prostatectomy pathological diagnosis in case 1 was adenocarcinoma Gleason score 4 + 5 = 9 (A, Hematoxylin–Eosin Stain, 200×). No small cell or large cell cancer tissue component was present. Immunohistochemical staining was positive for prostate-specific antigen (B, 200×) and synaptophysin (C, 200×). Only sporadic cells were positive for chromogranin A (D, arrowheads). The pathological diagnosis after prostate biopsy in case 2 was adenocarcinoma Gleason score 4 + 5 = 9 (E, Hematoxylin–Eosin Stain, 200×). Immunohistochemical staining for prostate-specific antigen (F, 200×) and synaptophysin (G, 200×) was positive

and he was referred to our department for further evaluation. The patient did not have a family history of PCa. In the past, 50 mg of naftopidil was administered for lower urinary tract symptoms, however, he did not have any urinary tract symptoms, and he was not taking any medications for BPH at the time of his first visit to our department. DRE revealed a stony-hard nodule in the left lobe of the prostate gland. The PSA level was 2.97 ng/ml, and the free-total PSA ratio was 11.1%. Serum NSE and pro-gastrin releasing peptide (Pro-GRP) levels were within normal limits. No lymph nodes or distant metastases were detected on the CT scan. The patient underwent a TRUS-guided transrectal prostate biopsy, and the pathological examination revealed an adenocarcinoma GS 4 + 5 = 9 in the left lobe (5 positive cores out of 12 cores) (Figure 2E). The ISUP grade was 5. Immunohistochemical staining for PSA (Figure 2F) and synaptophysin (Figure 2G) was positive. NSE and chromogranin A staining was negative. Cancer tissue was a typical adenocarcinoma, no small cell or large cell cancer tissue component was present, rejecting the diagnosis of primary NEPCa. The final pathological diagnosis was an adenocarcinoma. RRP as a treatment option was discussed with the patient and the family. The patient's Eastern Cooperative Oncology Group (ECOG)

performance status (PS) was grade 3, and he opted for maximal androgen blockade (MAB) with external beam radiation therapy (EBRT). MAB with leuprolide s.c. and bicalutamide 80 mg q.d. was initiated and the PSA level decreased to 0.005 ng/ml 7 months later. EBRT was scheduled to be performed later. The patients was evaluated monthly and then at trimonthly outpatient visits with biochemical profile and PSA.

3 | DISCUSSION

Prostate-specific antigen is secreted by the epithelial cells of the prostate and neoplastic prostate tissue. PSA is expressed in >95% of PCa cases.[8,9] Rare types of PCa do not present with high PSA levels.[10] These rare types of PCa cannot be diagnosed by PSA screening and are often diagnosed after the occurrence of symptoms. Moreover, there is no strict definition of "low PSA PCa". They are considered as PCa with PSA levels <10 ng/ml or, rarely, <4 ng/ml. Both patients presented here had initial PSA levels <3 ng/ml.

Relative amount of free or unbound PSA is lower in the serum of men with prostate cancer compared with those who have a normal prostate or BPH, which is reflected by low free/total PSA ratio. Free/total PSA ratio below 20% is improved the diagnostic accuracy of PCa.[11] The patients in this report had the ratio 9.6% and 11.1%, respectively.

Prostate cancer can be incidentally detected by pathological examination after radical cystectomy.[12] In this study, presence of prostate cancer shortened patients' survival with bladder cancer after radical cystoprostatectomy.[12] PCa can also be incidentally diagnosed after transurethral resection[13] or holmium laser enucleation of prostate for BPH. It might be also diagnosed by imaging technick for BPH,[14] other diseases[15] or imaging of metastatic disease in low PSA prostate cancer.[4–6]

Unusual histological types of PCa include mucinous adenocarcinoma, ductal cancer, basal cell PCa, and signet-cell cancer. PSA expression is highly prevalent in these tumors has a high prevalence (82.8%).[10] Ductal cancer is the second most common type of PCa. In one study, only one ductal adenocarcinoma was PSA-negative by immunohistochemistry among 29 unusual histological variants of prostate carcinoma.[10]

NEPCa is an aggressive and hormone-resistant subtype of PCa that presents with lower serum PSA levels. Small cell is the most common histological type of NEPCa. It accounts for <1% of all PCa cases. NEPCa can be either primary or treatment-emergent and the prognosis is worse for both types of NEPCa.[16,17] In one series, the proportion of patients with low serum PSA (0–4 ng/ml) PCas increased from 13.61% among adenocarcinomas to 17% in tumors with NE differentiation and was the highest among pure NEPCa (41%).[16] Conventional pathological examination has low sensitivity for the detection of NE features in biopsy or RRP specimens.[18] Although pathologically diagnosed as adenocarcinoma, GS 8–10 tumors with low PSA levels (≤2.5 ng/ml) are more likely to be associated with NE/small-cell genomic signatures.[19]

Recurrence and progression without elevation of PSA after RRP have also been reported.[20,21] The proportion of PSA-negative cases was higher in castration-resistant PCa (CRPC, 17.5%). Treatment-emergent NEPC (T-NEPC), an aggressive variant of CRPC, presents a higher fraction of PSA-negative cases (47.9%).[17] In these patients, cancer tissues presented with high-grade adenocarcinoma without an NEPCa cell component. The serum NSE and Pro-GRP levels did not increase. Immunohistochemical staining for NSE and chromogranin A staining was negative. However, the staining for synaptophysin (Figure 2C,G) was positive, which might indicate the presence of NE features in these tumors.

Low serum PSA levels are an independent negative prognostic factor in PCa.[16,17,19] PSA-negative PCa potentially responds poorly to androgen deprivation therapy (ADT).[19] A study using cell lines has demonstrated that cells that express low PSA levels or no PSA preferentially express stem cell genes. These cells are refractory to ADT and exhibit high clonogenic potential, thus, representing a critical source of castration-resistant PCa (CRPC).[22] Due to the potentially decreased sensitivity to ADT, prostatectomy is the treatment of choice for PCa with low serum PSA levels. Open RRP,[23] laparoscopic radical prostatectomy, and robotic-assisted radical laparoscopic prostatectomy are treatment options.[23,24] Pelvic lymph node dissection (PLND) is recommended for patients with a probability of lymph node invasion.[25] The first patient in this report underwent RRP with PLND and was free from recurrence 2 years and 6 months after the operation. The ECOG PS of the second patient was 3, and he opted for MAB with EBRT. Although PSA expression was confirmed in the prostate biopsy samples, there still was concern about the efficacy of ADT in this patient. PSA level declined and no progression was detected on the follow-up CT. Thus, despite low serum PSA levels, androgen receptor PSA axis was successfully targeted in this patient.

It is plausible to assume that low serum PSA levels may be caused by low PSA production by the tumor. In one study, 79 (11.2%) out of 702 patients who underwent radical prostatectomy had low serum PSA levels (0–4 ng/ml). However immunohistochemical staining revealed that 78 samples expressed PSA and only one sample with GS 5 + 5 = 10 was negative for PSA staining. No difference in PSA staining intensity was observed between the patients with low and high serum PSA levels.[26] Similarly,

other studies have demonstrated that PSA immunostaining does not correlate with serum PSA levels.[27,28] In both patients, the tumor tissues were positive in PSA staining (Figure 2B,F). Other factors including far lateral tumor location such as in these two patients, degree of microvessel density, and pattern of invasion may influence serum PSA levels. Other still unknown factors may also affect serum PSA levels in patients with PCa.

Low PSA (≤2.5 ng/ml) and high GS (8–10) tumors reportedly have higher expression of NE/small-cell markers and decreased AR activity.[19] Although both tumors presented here expressed synaptophysin, they were histologically diagnosed as adenocarcinomas. No small-cell or large-cell cancer tissue components were present. NSE immunohistochemical staining and serum NSE were negative.

Androgen deprivation therapy was not associated with a survival benefit in patients with low PSA levels (≤2.5 ng/ml) and high GS (8–10) who were treated with EBRT.[19] Thus, these tumors may be less responsive to ADT and surgery may be a more appropriate treatment strategy for these patients.[19] Case 1 was successfully treated with RRP. The ECOG PS of case 2 was grade 3 and the patient was unfit for surgery. The patient was started on ADT, and the PSA level decreased rapidly, indicating androgen receptor activity in the tumor cells.

4 | CONCLUSION

Clinically significant high-grade tumors can present with low serum PSA PCa. Such tumors are more likely to be associated with genomic features of NE. In the present two cases, the final pathological diagnosis was high-grade adenocarcinoma without NE differentiation. Low serum PSA PCa in both cases was incidentally diagnosed using contrast-enhanced CT scan. It is necessary to be cautious that any contrast-enhanced nodule in the prostate on a CT scan may present with PCa, irrespective of serum PSA levels. Such patients require a comprehensive urological examination.

AUTHOR CONTRIBUTIONS

SH, AW, RH, SI, and VB made substantial contributions to the conception and acquisition of data; VB conceived the study, reviewed the literature, analyzed and interpreted the data; SH, AW, and VB drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

This manuscript was completed in accordance with the ethical standards of the institutional research committee.

CONSENT

Written informed consent was obtained from the patients and their relatives for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in Chief of this journal upon request.

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