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**CASE REPORT**

**Diagnosis of high-grade prostate cancer in patients with unexpectedly low prostate specific antigen levels: a rare case series**

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**ABSTRACT**

**Background:** Prostate cancer is regarded as one of the most common leading causes of male cancer-related death worldwide. Clinicians agree that prostate specific antigen (PSA) is the best prostate cancer predictor. High PSA levels increase prostate cancer risk in most men. However, other research suggests that prostate cancer with low PSA levels is aggressive. In this uncommon case series, we present three high-grade prostate cancer patients with low PSA.

**Case Description:** Between 2018 and 2019, three patients were referred for further therapeutic management after initial evaluation and treatment from secondary hospitals. All patients underwent complete diagnostic procedures including Laboratory examination, Pathological examination, and Radiologic imaging. PSA levels were 0.67 ng/mL, 4.0 ng/mL, and 4.93 ng/mL in the first, second, and third patients, respectively. The first two of three patients had a Gleason score (GS) of 9 (5+4), and one patient presented with GS of 8 (5+3). Distant metastatic disease was not found in our series. All of the patients underwent hormonal therapy, and none of them underwent radical prostatectomy. Follow-ups were completed in all patients, with the survival of 3 months, 4 months, and 12 months respectively.

**Conclusion:** High-grade prostate cancer in patients with low PSA levels emphasizes the need for rigorous history taking and physical examination and quick investigation of new biomarkers and criteria for prostate cancer detection. These patients' prognosis and optimal therapy are unknown. These patients have a worse prognosis than those with high PSA values, according to multiple studies.

**Keywords:** case series, prostate cancer, antigen, diagnosis.

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**INTRODUCTION**

Prostate cancer is the second most common malignancy in men and the leading cause of death in men. Prostate cancer cases with low PSA levels are very rare, representing less than 1% of all metastasized prostate cancer patients.¹

Prostate cancer is a disease which incidence is age dependent. Approximately 1.1 million cases worldwide in 2012 accounted for 15% of all cancers diagnosed.¹² The incidence of prostate cancer varies widely between different geographical regions, being highest in Australia or New Zealand, North America, Western Europe, and Northern Europe, mainly detected due to PSA testing and an increasingly elderly population. The incidence is low in East, South, and Central Asia, while in Eastern and Southern Europe, it has steadily increased.³

PSA has a high predictive value as a screening tool to detect early prostate cancer. The use of a PSA threshold of 4.0 ng/ml in men over 50 has been widely accepted among clinicians. However, the prevalence of prostate biopsies with PSA values of 4.0 ng/ml or lower or other indications (e.g., abnormalities on digital rectal examination) is still minimal.³

Prostate cancer with low PSA levels is a rare case. The prevalence of prostate cancer increases with PSA value. In one study, 7% of prostate cancers in men had a PSA of 0.5 ng/ml or less, and 27% of prostate cancers in men with a PSA of 3.1 - 4.0 ng/ml. Furthermore, the prevalence of high-grade disease also increases with PSA value.⁴

In this case series, we report three high-grade prostate cancer patients presenting with low levels of PSA. This case series has been reported in line with the PROCESS Guideline.⁵

**PRESENTATION OF CASES**

**Case 1**

A 54-year-old man was referred from Ibnu Sina Gresik Hospital to the Urology outpatient clinic of Dr. Soetomo Hospital with a diagnosis of prostate cancer after Transurethral Resection of the Prostate (TURP) surgery. The patient's main complaint was urine accompanied with blood clots for one year. Since 2015, the patient has complained that urination is often interrupted, accompanied with pain, and the patient has sensation like cannot fully empty the bladder.

The symptoms were getting worse, and finally, the patient complained that he could not urinate one month before surgery. The patient also complained of pain in the joints and bones, especially in the spine area. Finally, the patient was treated by a urologist, and TURP surgery was performed in August 2018. The patient

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had a history of smoking for 25 years. The patient denied any family history of cancer. The patient had no history of high blood pressure and diabetes.

On physical examination, the patient was in general fair condition, and fully conscious. Blood pressure of 115/73 mmHg, pulse of 73 beats per minute, spontaneous breathing with 20 breaths per minute, and axillary temperature of 36.8°C. General status was within normal limits. From urological examination, there is no mass or tenderness in the right and left flank region, empty bladder on palpation, spontaneous micturition with urine production of 2000 cc per 24 hours clear yellow. External genitalia examination was within normal limits. On digital rectal examination, the prostate was found to be solid and hard, asymmetrical, and the surface was lumpy (nodules).

The initial laboratory examination found that the hemoglobin level was 11.5 g/dL, leukocytes 11 x 10³ /uL, and platelets 579 x 10³ /uL. Renal function with blood urea nitrogen (BUN) of 9 mg/dL and serum creatinine of 1.33 mg/dL. The serum electrolyte examination showed sodium of 142 mEq/L, potassium of 4.9 mEq/L, and chloride of 98 mEq/dL. Liver function examination obtained SGOT 17, SGPT 24, and albumin level of 3.8 mEq/L. Urinalysis showed pH 5.5, microhematuria, and sterile urine culture results. Hemostasis function examination is within normal limits. The PSA examination showed 0.67 ng/ml and a testosterone level of 395.18 ng/dL. The urodynamic study obtained Q max 26.9 ml/s and voided volume 132 ml, residual urine after micturition 81.6 cm³. The results of the pathology anatomy examination concluded Acinar adenocarcinoma, Gleason score 9 (5 + 4) the tumor grew to the periprostatic fatty tissue.

The chest plain x-ray photo did not find any metastatic processes in the lungs and bones in the thoracic region. A plain abdominal x-ray shows destruction of lumbar vertebra 5 (VL 5) (Figure 2). A bone scan examination of the skull and extremities found no signs of metastasis. Abdominal ultrasound found a solid heteroechoic lesion, indistinct boundaries, and irregular lesion edges with a size of 3.76 x 5.39 x 3.18 cm in the prostate (Figure 3), with the help of color duplex sonography (CDUS) appearing intralessential vascularity. The lesion extended superiorly and infiltrated the inferior to the posterior wall of the bladder. There was no metastatic process in other organs.

From interdepartmental consultation, the Cardiology Department assessed this patient with Cardiac Risk Index (CRI) class I. The patient was diagnosed with Prostate Adenocarcinoma with Gleason Score 9 (5+4) with clinical stage T3a (Tumor on microscopic perivesical tissue) Nx (Regional lymph nodes cannot be assessed) M1 (metastases to lumbar vertebra V). The patient passed away after three months of follow-up.

Case 2

A 61-year-old man was referred from Bangkalan Regional Hospital by an Internal Medicine specialist to the Emergency Department of Dr. Soetomo General
Hospital, with complaints of difficulty urination and hematuria. Complaints of difficult urination were experienced by the patient one month prior. Before, the patient complained of frequent urination, feeling unsatisfied after urination, and a burning sensation while urinating. The patient was admitted for one week to Bangkalan Regional Hospital and treated by an internal medicine doctors, but the patient's symptoms did not improve. The patient was then referred to the Emergency Department of Dr. Soetomo General Hospital with a diagnosis of Benign Prostate Enlargement and hematuria.

On physical examination, the patient was in fair condition, fully consciousness, blood pressure of 110/80 mmHg, pulse of 87 beats per minute, spontaneous breathing with 18 breaths per minute, and axillary temperature of 36.8°C. General status is within normal limits with urological status not found masses or tenderness in the right and left lumbar region, empty bladder impression, spontaneous micturition with urine production of 1100 cc per 24 hours reddish. External genitalia examination revealed no abnormalities. On digital rectal examination, the prostate was found to be solid and hard, asymmetrical, and the surface was lumpy (nodules).

Laboratory examination on the blood sample revealed hemoglobin level of 10 g/dL, leukocytes of 21 x 10^3 /uL, and platelets of 381 x 10^3 /uL. Renal function BUN of 33 mg/dL and serum creatinine of 1.51 mg/dL. Serum electrolyte examination results; sodium of 131 mEq/L, potassium of 4.36 mEq/L, and chloride of 97.6 mEq/L. Liver function examination SGOT 19, SGPT 22, Albumin 3.0 mEq/L. Urinalysis obtained pH 5.0, hematuria, and sterile.
urine culture results. Hemostasis function examination is within normal limits. PSA examination was found to be 4.93 ng/ml.

Radiological examination of anteroposterior and lateral thoracic x-ray photos did not reveal any metastatic process in the lungs and bones in the thoracic region. Abdominal plain photographs showed no metastatic processes in the visualized bones. Abdominal ultrasound showed an enlarged prostate volume with a volume of ± 45 ml. There was a heteroechoic mass with a size of 7.2 x 4.72 x 6.3 (volume ± 113 ml) on the posteroinferior wall of the bladder, which on post spooling the impression of size decreases, suspicious bladder mass accompanied by blood clots (Figure 5). A Bosniak 1 left renal cyst was found.

Based on the urology duty report results, the patient decided to undergo cystoscopy, clot evacuation, and TURP. From the results of laboratory examination of anatomical pathology of TURP tissue, it was found that prostate adenocarcinoma, Gleason score 9 (5 + 4), did not appear as perineural invasion.

The patient was diagnosed with Prostate Adenocarcinoma with Gleason score 9 (5+4) with clinical stage T1b (Tumor accidentally found on histopathology more than 5% resection tissue) Nx (Regional lymph nodes cannot be assessed) M0 (No distant metastasis). The patient and her family wanted non-surgical treatment. Then, the patient took Leuprorelin acetate 11.25 mg (LHRH agonist) and bicalutamide 50 mg (non-steroidal anti-androgen). The patient refused and wanted non-surgical treatment. Then, the patient was planned to undergo hormonal therapy.

**DISCUSSION**

PSA is a prostate cancer serum marker and a strong predictor for prostate cancer detection. PSA breaks down seminal fluid semenogelin I and II in prostate acinar and ductal epithelial cells. Metastatic prostate cancer patients almost always have high serum PSA. Patients with metastatic prostate cancer and a low PSA account for less than 1% of the total prostate cancer patient population. Gleason score > 7, unusual histological variants, including small cell and ductal carcinoma, anaplastic, and locally progressed tumors are common in patients with low PSA levels. Low-risk patients rarely progress despite low PSA levels (e.g., those on T1 with a GS of 5 or 6). Occurrences of prostate cancer without an increase in PSA remain a mystery. According to some literature, this phenomenon may be caused by prostate cancer cells that cannot make PSA (e.g., tiny cells, neuroendocrine tumors) or are poorly differentiated and lose their ability to do so. In the three cases above, prostate cancer was diagnosed by TURP tissue, not routine screening as per EAU standards. After that, nodules and metastases were diagnosed.

The first patient had a PSA of 0.67 ng/ml and a Gleason score of 9 (5+4). The patient took Leuprolrelin acetate 11.25 mg (LHRH agonist) and bicalutamide 50 mg (non-steroidal anti-androgen). The patient died 3 months later. From the radiology examination, there were lytic lesions on the fifth lumbar vertebra (Figure 2), consistent with the literature that high-grade prostate cancer tends to spread to the bone. Hussain et al. found...
that most prostate cancer metastases were in the bone (84%), distant lymph nodes (10.6%), liver (10.2%), and lung (9.1%).

Gregory R. Pond et al. found that prostate cancer patients with bone-only metastases (median OS 19.0 months) and bone-and-lymph node metastases (median OS 15.7 months) had longer survival times.16 Liver metastases with or without lymph node or bone metastases had the worse prognosis (median OS 10.0 months) (median OS 14.4 months). According to Susan Halabi et al., visceral metastases have a worse prognosis than bone metastases. It may be because visceral organs are more important for metastases than bones.11

In the second example, a 61-year-old patient had a PSA of 4.0 ng/ml and a Gleason score of 9 (5+4). Patient and family oppose surgery. After an uro-oncology conversation in November 2018, the patient underwent androgen deprivation therapy (ADT) with an LHRH agonist injection (Leuprolelin acetate 11.25 mg) every three months and oral non-steroidal anti-androgens (bicalutamide 50 mg). The patient did not have lymph node (N) or organ metastases (M). The patient regularly visits the polyclinic for consultations. The patient died four months after diagnosis.

The third patient had a blood PSA of 5.3 ng/ml and a glass score of 9 (5+4). The patient and family refused radical prostatectomy based on the uro-oncology discussion, the patient underwent hormonal therapy with leuprolelin acetate 11.25 mg (LHRH Agonist) injections every three months and bicalutamide 50 mg tablets (non-steroidal anti-androgens). The Patient visit the polyclinic regularly for consultation and taking drugs for hormonal therapy and experienced no new symptoms during hormonal therapy. The patient died one year after the diagnosis.

In a study comparing prostate cancer patients with low PSA and high Gleason scores, radical prostatectomy had better OS than EBRT and EBRT + BT. Radical prostatectomy and EBRT + BT had lower PCSM than EBRT. (14) PSA is a prostate cancer biomarker. A marker of prostate cancer status is metastatic hormone-sensitive prostate cancer (mHSPC) or metastatic castration-resistant prostate cancer (mCRPC) with testosterone castration levels or radiological progression of more than two bone or soft tissue lesions.

The patient has small-cell or neuroendocrine prostate cancer. Small cell carcinoma of the prostate accounts for 0.5% to 2% of malignant prostate cancers. 50% of prostate adenocarcinomas are accompanied by small cell carcinoma. 5% to 10% of adenocarcinomas have neuroendocrine differentiation. This aggressive cancer is usually diagnosed late because there is no PSA elevation. Neuroendocrine prostate cancer (NEPC) is under-recognized due to tumor heterogeneity, a limited number of biopsies on metastatic tumors, a lack of a uniform consensus definition based on histology or biomarker expression, and frequent misclassification of high-grade adenocarcinoma prostate cancer, especially those of mixed histology. Prostate adenocarcinoma can histopathologically transform. They have clinical features, relevance, and prognosis. Small cell, squamous, sarcomatoid, urothelial, basal cell, and adenoid cyst. This is due to prostate adenocarcinoma differentiation or metaplasia. In these cases, the amount of adenocarcinoma in prostate cancer affects PSA.12

Given the biological heterogeneity and multifocality of prostate cancer, there is a high probability of clonal shifts in a high-grade Gleason tumor that express small-cell prostate cancer features, including aggressive biology and reduced PSA production. Kim YW et al. reported this in prostate adenocarcinoma patients with a PSA of 30.3 ng/ml. Seven months later, the patient was diagnosed with adenosquamous carcinoma of the prostate.13 Cecen K reported a similar case in 2014 in a patient who was initially diagnosed with prostate adenocarcinoma T2N0M0, Gleason scores 7 (3+ 4), and a PSA value of 23 ng/ml, but then changed to small cell carcinoma with a normal PSA value.15 This contradicts the idea that PSA is the most sensitive marker for prostate cancer and that no other tests are needed when PSA is low or undetectable. In patients with high-grade prostate cancer, especially an atypical variant, periodic imaging should be considered even if the PSA level is low.

In such patients, assaying neuron-specific enolase, carcinoembryonic antigen, or CA 19-9 may provide early cancer evidence. Even with undetectable or low PSA levels, prostate cancer can metastasize. Even when PSA levels are low, additional serum tumor markers and imaging studies may be considered for patients with undifferentiated tumors and atypical cancer variants. Sella et al. reported 18 patients with neuroendocrine tumors or a combination of adenocarcinoma and prostate cancer sample cells and metastases.8 Each patient had an increase in CEA, CA 19-9, CA 15-3, or CA 125.16 All specimens showed neuroendocrine immunoreactivity. Visceral metastases, lytic lesions in the bones, cisplatin sensitivity, and small cell type or poorly differentiated adenocarcinoma are prostate cancer characteristics.15,16,17

Primitive prostate stem cell tumors can metastasize to the lungs, liver, brain, or bone but don't express PSA. These tumors express embryonal or neuroendocrine markers (neuron-specific enolase or chromogranin A).18 Early progenitor stem cells can migrate, invade, and metastasize into different tissues, according to Tu et al. Progenitor stem cells have limited metastatic ability and a homogeneous phenotype.19 Unfortunately, the primary tumor and its metastases couldn't be reexamined. Other tumor marker tests haven't proven this. The patient's prognosis is also poor, likely due to variants of prostate cancer.

Docetaxel or carboplatin with docetaxel is used in prostate adenocarcinoma with neuroendocrine differentiation. (16) A single-arm phase II study tested carboplatin, docetaxel, and prednisone in 113 patients with anaplastic or aggressive prostate cancer. (1) Prostate small cell carcinoma on histology (SCCP) (2) Visceral metastases (5) Low PSA (10 ng/mL) and high volume (>20) bone metastases (6) immunohistochemistry, chromogranin, synaptophysin staining or elevated neuroendocrine markers plus elevated LDH, CEA, or malignant hypercalcemia (7) short-interval (6 months) response to primary ADT. After carboplatin plus docetaxel failed, cisplatin plus etoposide was used. After 4 cycles of carboplatin plus docetaxel...
and cisplatin plus etoposide, 65.4% and 33.8% of patients were progression-free, respectively. Continued platinum-based chemotherapy with etoposide can be considered second-line therapy. Because of its tendency to metastasize, pure small-cell prostate cancer (SCCP) is treated with chemotherapy and radiotherapy. Aggressive patients receive platinum-based chemotherapy first. No literature differentiates the management of low PSA prostate cancer patients from general prostate cancer. Staging and progression guide treatment.

CONCLUSION
The incidence of high-grade prostate cancer in individuals with low PSA levels emphasizes the requirement of careful history taking and physical examination and necessitates the quick investigation of new biomarkers and measures for diagnosing prostate cancer. At the present time, the prognosis of these patients is still unknown, and there is no general agreement regarding the treatment that is most effective for this particular set of patients. On the other hand, a number of studies have shown that the prognosis for these people is worse than the prognosis for patients whose PSA levels are high.

CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest.

INFORMED CONSENT

REFERENCES