Case Report

Novel case of androgen receptor-positive cancer of unknown primary without serum prostate-specific antigen elevation that became progression free in the long term after primary combined androgen blockade

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Abbreviations & Acronyms
ADT = androgen deprivation therapy
AR = androgen receptor
CAB = combined androgen blockade
CRPC = castration-resistant prostate cancer
CT = computed tomography
CUP = cancer of unknown primary
HCV = hepatitis type C virus
MRI = magnetic resonance imaging
NCCN = National Comprehensive Cancer Network
PSA = prostate-specific antigen

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Introduction: The prognosis of cancer of unknown primary is very poor. Such a prognosis can be improved by characterizing primary characteristics and developing tailored site-specific therapy, especially for androgen receptor-positive adenocarcinoma. However, in such cases without elevated prostate-specific antigen, the efficacy of androgen deprivation therapy is unclear.

Case presentation: Herein, we report a case that presented with a retroperitoneal cancer of unknown primary that was confirmed as an androgen receptor-positive adenocarcinoma without prostate-specific antigen elevation. Pelvic magnetic resonance imaging did not reveal any suspicious cancer lesions in the prostate. Furthermore, malignant cells were not present in a prostate biopsy specimen. In spite of the prostate-specific antigen level, on the basis of immunohistochemical analyses, including NKX3.1, the patient was first treated with androgen deprivation therapy, leading to long-term progression-free survival.

Conclusion: Early androgen deprivation therapy based on immunohistochemical analyses might lead to a good outcome in androgen receptor-positive adenocarcinoma cancer of unknown primary patients regardless of prostate-specific antigen level.

Key words: androgen receptor, cancer of unknown primary, NKX3.1.

Keynote message

On the basis of immunohistochemical analyses, including NKX3.1, early ADT should be performed in the case of AR-positive CUP adenocarcinoma patients regardless of PSA levels.

Introduction

When widespread metastatic disease occurs in the absence of an identifiable primary tumor site after intensive investigation this is known as a CUP. Worldwide, the incidence of CUP is approximately 5% of all cancers, and the prognosis is very poor.[1,2] Accurate identification of the tissue characteristics of origin and subsequent site-specific treatment might improve survival. Recent guidelines, therefore, recommend that the serum PSA level be measured in men aged over 40 with adenocarcinoma, and that ADT be undertaken on the basis of the immunohistochemical analyses of protein profiles, including AR.[3] However, in the case of adenocarcinoma without PSA elevation, the efficacy of ADT is unclear.

Case presentation

A 60-year-old Japanese male was referred to the Department of Gastrointestinal Surgery after the incidental detection of a retroperitoneal tumor without symptoms. The patient had a previous history of HCV infection; however, no abnormalities existed on hematological

examination and an anti-HCV antibody test was negative. Contrast-enhanced abdominal CT revealed around 25-mm-sized retroperitoneal tumor with heterogeneous enhancement on the left of the aorta (Fig. 1a–c). MRI demonstrated that the tumor exhibited iso-signal intensity on T1-weighted images, moderate-to-high intensity on T2-weighted images, and high intensity on diffusion-weighted images (Fig. 1d–f). After informed consent, the tumor was surgically removed. In addition, pathological findings revealed a fused glandular neoplasm composed of enlarged cells with atypical nuclei (Fig. 2a,b). An immunohistochemical profile included positive results for AR (Fig. 2c), PSA (Fig. 2d), and NKX3.1 (Fig. 2e), and negative results for cytokeratin 7, cytokeratin 20, thyroid transcription factor 1, CDX-2, chromogranin A, CD3, CD20, estrogen receptor, progesterone receptor, hepatocyte-specific antigen, and prostate-specific membrane antigen (Fig. 2f). Histopathological findings revealed a poorly differentiated adenocarcinoma in which the MIB-1 index, determined by the number of Ki67-positive cancer cells, was 28.5% (Fig. 2g). These results suggested the primary site of the tumor was the prostate, and, therefore, the patient was referred to our department. The patient's serum PSA level was 3.67 ng/mL, and a digital rectal examination was unremarkable. Other serum tumor markers, including β-chorionic gonadotropin, cancer antigen 19-9, and carcinoembryonic antigen, were within normal range. ^{18}F-fluoro-deoxyglucose positron emission tomography did not show abnormal uptake in the prostate or other organs (Fig. 3a,b). Three-Tesla MRI revealed a normal prostate without a cancerous lesion (Fig. 3c). An ultrasound-guided 12-core transperineal systematic prostate biopsy revealed no malignant cells. Therefore, the patient chose no further treatment. However, 3 months later, CT revealed multiple lymph node swellings, including in left supraclavicular and para-aortic sites (Fig. 3d,e); the PSA doubling time was 6.9 months. On the basis of a final diagnosis of CUP, the patient underwent CAB therapy as ADT, including a luteinizing hormone-releasing hormone antagonist and 80 mg of bicalutamide after obtaining the approval of the institutional cancer board. His serum PSA quickly reached a nadir level without any adverse events; 3 months after the initiation of ADT, all lymph node swellings had disappeared on CT (Fig. 3f,g). The patient

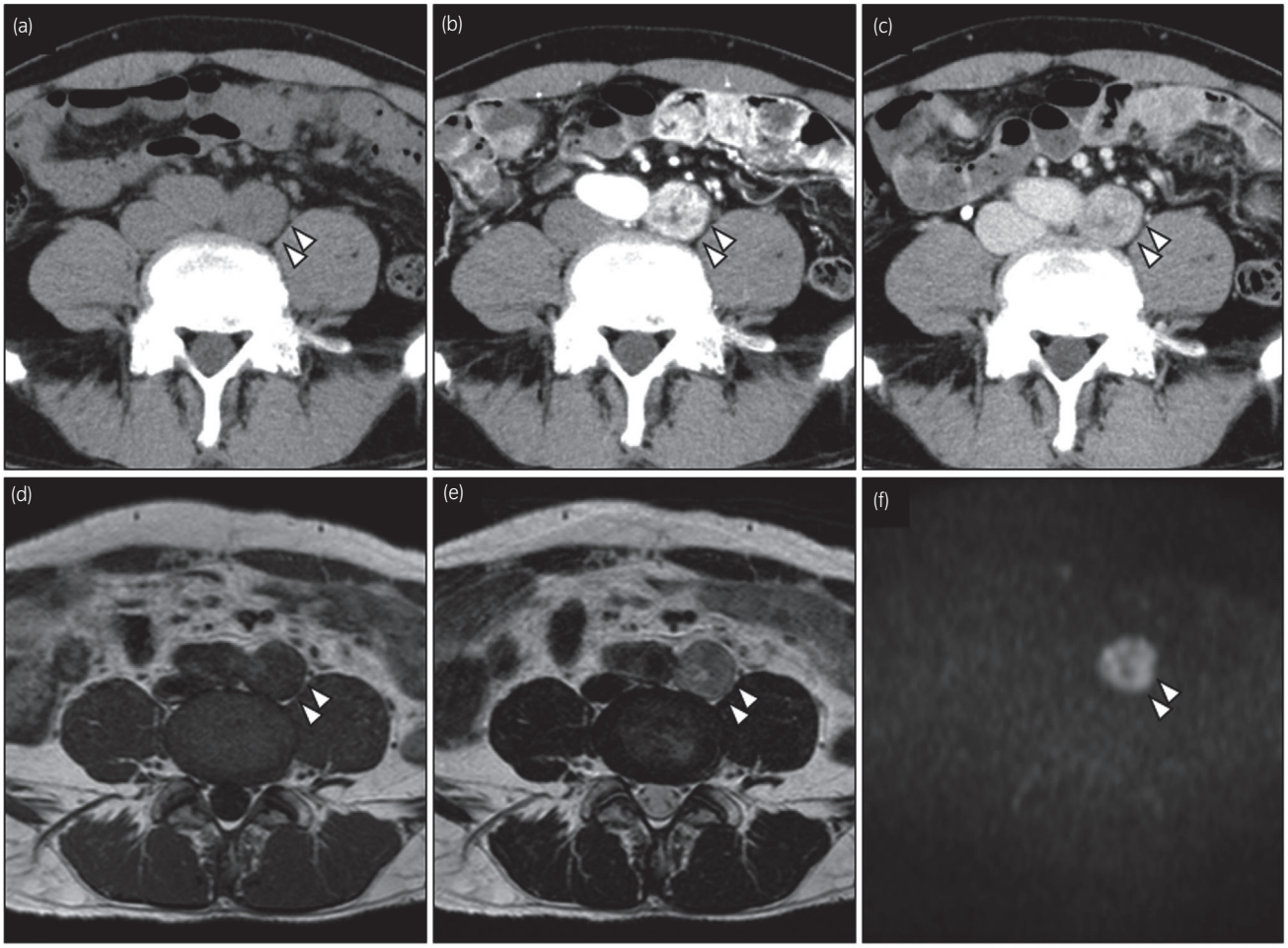

Fig. 1 (a) Axial unenhanced CT demonstrates a well-defined, 25-mm soft tissue mass in the left para-aortic region (arrowheads). (b) Arterial and (c) venous phase IV contrast-enhanced CT images show avid, heterogeneous enhancement in the arterial phase followed by mild washout in the venous phase. The mass exhibited iso-signal intensity on (d) T1-weighted images, (e) moderate-to-high signal intensity on T2-weighted images, and (f) high signal intensity on diffusion-weighted images on MRI.

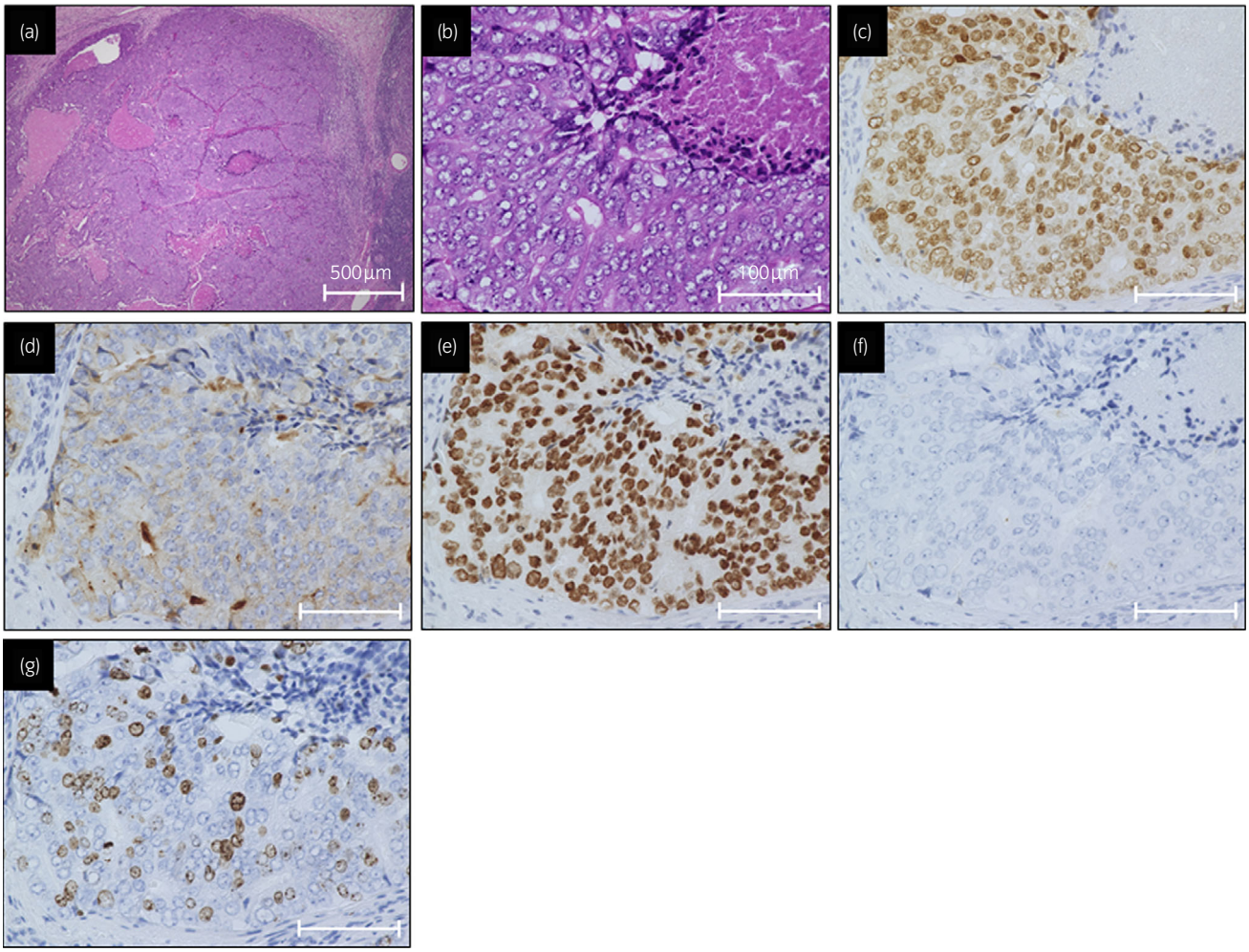

Fig. 2 HE and immunohistochemical staining of the retroperitoneal tumor. (a,b) An adenocarcinoma consisting of the tubular proliferation of columnar-shaped tumor cells. The tumor cells were positive for (c) NKX3.1, (d) PSA, and (e) AR and (f) negative for PSMA. (g) The MIB-1 index calculated by Ki67-positive cancer cells was 28.5%.

successfully showed progression-free survival for 4 years with continuous primary CAB as an outpatient.

This study was approved by the Nagoya City University Graduate School of Medical Sciences Institutional Review Board (#60200039). Written informed consent was obtained from the patient for publication of this article and accompanying images.

Discussion

CUP occurs fairly equally in males and females, with an average age at diagnosis of 60 years. Common sites of involvement include the liver, lungs, bones, and lymph nodes, with metastasis occurring to any site.[1–4] The median overall survival is about a year, and evidence-based treatment by accumulated prospective data is lacking. Hence survival has not improved. One reason for a poor prognosis is that CUP consists of heterogeneous tumors and has a wide variety of clinical presentations in most patients. NCCN guidelines for CUP suggest diagnostic examinations based on tumor site and a patient's gender.[3] Above all, a male aged >40 years with an adenocarcinoma of unknown primary should undergo testing for serum PSA and subsequent site-specific treatment.[5–7] However, diagnostic examinations are not suggested when patients do not show an elevated PSA level. For most patients with CUP, recommended treatments include radiation therapy or systemic chemotherapy, including a combination of taxane derivatives and platinum regimen, or a gemcitabine and platinum regimen.[3] On the basis of immunohistochemical analyses, we first selected ADT with which a good prognosis was obtained in spite of a normal PSA level. Recent evidence has been emerged supporting the use of ADT for head–neck adenocarcinomas that express AR.[8] Considering the clinical course of this case, first-line ADT may have led to a better prognosis.

When considering metastatic adenocarcinoma of unknown origin, PSA is commonly used as a marker to identify prostate carcinomas. However, PSA is also expressed in non-prostate tumors, including in the breast and salivary glands.[9,10] Gurel *et al.* recently reported that NKX3.1 protein is expressed in many primary metastatic cancers of prostate origin that are untreated.[11] *NKX3.1* is an androgen-regulated

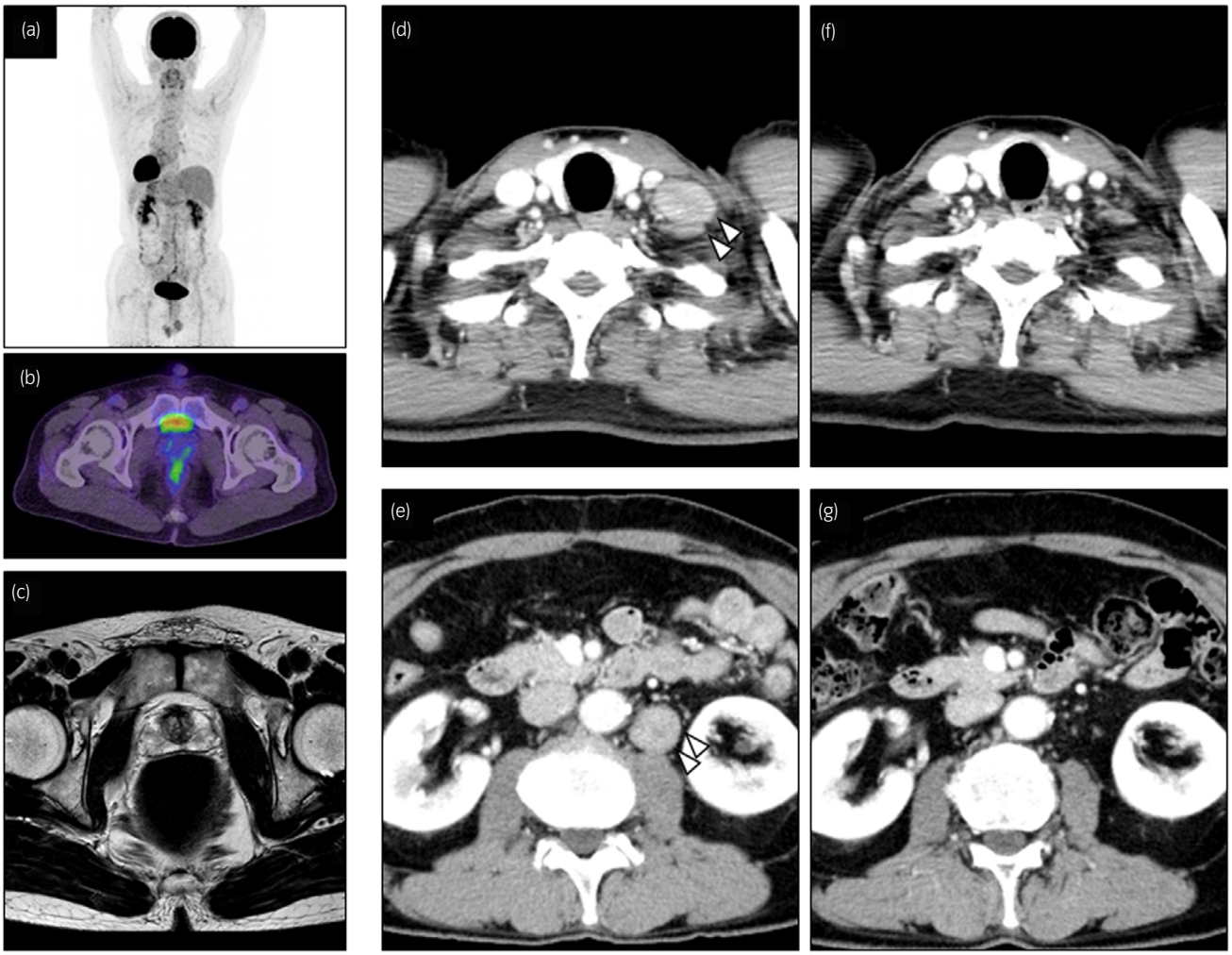

Fig. 3 ^{18}F-Fluorodeoxyglucose positron emission tomography/CT did not show abnormal uptake in (a) other organs and (b) the prostate on a whole-body scan. (c) Prostate MRI did not show a significant abnormality. CT images showed recurrences in (d) the supraclavicular and (e) para-aortic nodes 3 months after the resection of the primary lesion. (g) A follow-up CT showed a significant reduction of the lesions after an 18-month CAB therapy.

prostatic tumor suppressor gene expressed predominantly in prostate epithelium; NCCN guidelines recommend immunohistochemical testing in patients with adenocarcinoma and retroperitoneal CUP. In this case, although tumor markers, including PSA, were not examined before surgical resection, MRI did not reveal any suspicious cancer lesion in the prostate; furthermore, malignant cells in a prostate biopsy specimen were not found. Although the CT study showed strong early phase enhancement and delayed washout, which is one of characteristic findings of prostate cancers, it was still considered difficult to make a definitive diagnosis. Therefore, even in a case with no origin site in the prostate, the analysis of protein levels, including NKX3.1, can contribute to an early diagnosis and medical intervention.

In this case, because of ADT, long-term progression-free survival was successfully obtained. However, in the face of recurrence or a refractory cancer, such as CRPC, salvage therapy is not established. Nowadays, with respect to the control of prostate cancer, CRPC is known to not be completely androgen independent. In this regard, several drugs designed to further suppress the AR pathway have shown improved survival, including abiraterone acetate and enzalutamide.[12] However, the efficacy of such drugs is limited, with approximately 20–40% of patients with CRPC showing a poor clinical response. In such cases, in addition to the mutation and amplification of the AR, spliced variants of the AR protein, such as AR splice variant 7 that lacks a functional ligand-binding domain, have been reported as major resistance mechanisms in CRPC.[13] Based on the accumulated data of CUP cases, including our case, the establishment of systematic treatments based on genetic profiles needs to be elucidated in future.

Conclusion

We report here a case of AR-positive adenocarcinoma without PSA elevation that showed long-term progression-free survival after primary ADT. Immunohistochemical analyses, including NKX3.1, should be performed regardless of serum PSA levels. Early ADT, including CAB, may lead to a good outcome. However, further investigation of this rare disease is required.

Conflict of interest

The authors declare no conflict of interest.

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