Case Report

Small cell neuroendocrine prostate cancer with adenocarcinoma components—case report and literature review

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Background: Small cell neuroendocrine prostate cancer (SCNC) is a rare aggressive type of neuroendocrine prostate cancer (NEPC) characterized by aggressive clinical course and lack of response to hormone therapy.

Case Description: We present a case report of a 60-year-old man diagnosed with a histologically confirmed primary metastatic (bone, lymph nodes and visceral) SCNC with small components of an adenocarcinoma with clinical symptoms mimicking an acute prostatitis. Of note, serum based neuroendocrine markers (carcinoembryonic antigen, chromogranin A) were negative and the patient had a prostate-specific antigen (PSA) elevation. Genetic testing of tumor tissue revealed breast cancer gene 2 (*BRCA2*) copy number loss and a retinoblastoma gene (*RB1*) mutation reflecting again the aggressiveness of the disease. Germline testing for the *BRCA2* copy number loss was unremarkable. After 6 cycles of carboplatin and etoposide in combination with androgen deprivation therapy (ADT) the Eastern Cooperative Oncology Group (ECOG) performance status has improved from 3 to 0, in addition the patient was free of pain. In line with clinical improvement, both prostate-specific membrane antigen (PSMA) and fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) revealed a significant reduction of metastatic load. Currently, the patient is treated with ADT plus apalutamide.

Conclusions: We demonstrate for the first time a case of a primary metastatic SCNC with adenocarcinoma components successfully treated by the combination of platinum-based chemotherapy plus hormonal therapy. In addition, we provide a literature overview on management of SCNC as there is no standard treatment established for this disease.

Keywords: Case report; chemotherapy; neuroendocrine prostate cancer (NEPC); prostatitis; small cell prostate carcinoma

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Introduction

Prostate cancer is most common non-cutaneous malignancy, accounting for the second common cancer-related cause of mortality in western countries (1).

Small cell neuroendocrine prostate cancer (SCNC) is a rare but highly aggressive phenotype of neuroendocrine prostate cancer (NEPC). *De novo* SCNC arises in less than 1% of prostate cancer cases (2). More commonly NEPC is a result of transformation from adenocarcinoma during treatment with either 2° generation androgen receptor targeting agents (abiraterone, enzalutamide) or taxane-based chemotherapeutic agents. This transformation occurs in up to 25% of patients with metastatic castration resistant prostate cancer (mCRPC) (3). In contrast to adenocarcinoma, NEPC do not express prostate-specific antigen (PSA), leading to the fact that NEPC cannot be detected in PSA-based early detection programs. As NEPC generally loses prostate-specific membrane antigen (PSMA) expression, PSMA-based imaging can be inaccurate, claiming for the use of fluorodeoxyglucose-positron emission tomography (FDG-PET) (4).

Median survival of patients with SCNC has been reported of being 18 months with a range between 12 and 60 months. Of note, an age of <60 years, radical prostatectomy with adjuvant radiation therapy, absence of the metastasis and a mixed low-grade prostate adenocarcinoma are considered to be favorable prognostic factors (5). We present this article in accordance with the CARE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-541/rc).

Highlight box

Key findings

- We demonstrate a case of a primary metastatic small cell neuroendocrine prostate cancer (SCNC) with adenocarcinoma components successfully treated by the combination of platinum-based chemotherapy plus hormonal therapy.

What is known and what is new?

- SCNC is rare and aggressive type of cancer, which progresses rapidly. Currently there is no standard of treatment and the chemotherapy with etoposide and platinum-based agents is used.
- Genetic testing of tumor tissue revealed breast cancer gene 2 (*BRCA2*) copy number loss and a retinoblastoma gene (*RB1*) mutation reflecting again the aggressiveness of the disease.

What is the implication, and what should change now?

- Despite initial response, the standard of care fails to improve the outcome of patients with SCNC. More research is needed to find out new therapy options for the patients with SCNC.

Case presentation

A 60-year-old man presented in November 2022 with Eastern Cooperative Oncology Group (ECOG) status 3 at the emergency department with pain in the left lower quadrant of the abdomen with projection in the groin and frequent micturition, persisting for one week. The patient was regularly undergoing urological check-ups, the last one being three weeks ago. A consequently performed ultrasound and computed tomography (CT) scan showed a central necrotic formation in peripheral zone of the prostate with approximately 2 cm in diameter, which was interpreted as prostatitis. Elevated levels of C-reactive protein (CRP) of 7.89 ng/mL and dolent prostate during digital rectal examination were matching the diagnosis. Enlarged lymph nodes in the left groin were interpreted as post inflammation genesis. Thus, the patient was diagnosed with prostatitis and an antibiotic therapy with ciprofloxacin was prescribed for two weeks. However, sonographic re-evaluation after one month still confirmed the 4 cm hypoechoic, partially hyper-vascularized lesion in the peripheral zone of the prostate, perforating the capsule. In addition, further elevated PSA of 30 ng/mL was observed. Consequently, a pelvic multiparametric magnetic resonance imaging (mpMRI) was performed. Prostate Imaging Reporting and Data System (PI-RADS) V lesion was described with a tumor, perforating the capsule and infiltrating the left seminal gland and neurovascular bundle. These findings led to prostate biopsy, revealing not only SCNC in 8/15 cores, but also an ISUP 1 adenocarcinoma lesion of less than 0.1 cm in one core (*Figure 1A*). The diagnosis was confirmed by two independent pathologists. Of note, immunohistochemical staining was negative for CK20 and Synaptophysin and partially positive for CD56 (*Figure 1B,1C*). Ki-67 expression was up to 80% (*Figure 1D*). Moreover, hematoxylin and eosin staging confirmed the classic neuroendocrine morphology including finely granular chromatin, high nuclear-to-cytoplasmic ratio, inconspicuous nucleoli and nuclear molding (*Figure 1E,1F*).

By that time PSA level almost doubled to 72 ng/mL with a lactate dehydrogenase (LDH) level of 501 U/L (normal range, 100–250 U/L), while neuroendocrine tumor markers such as CA19-9, and carcinoembryonic antigen (CEA) and chromogranin were not elevated. Staging was performed using a whole body contrast enhanced CT, a bone scan

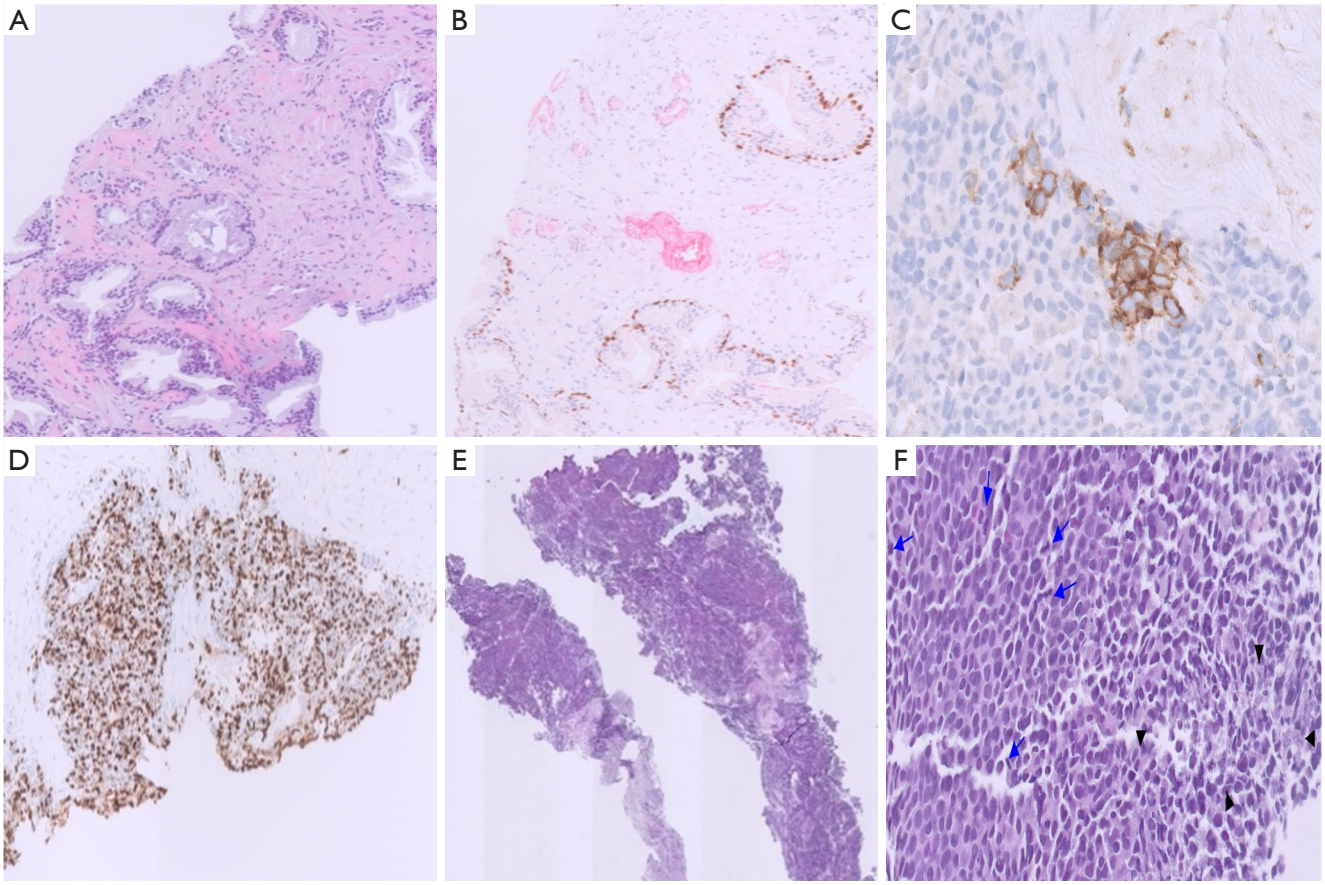

Figure 1 Microscopic examination of the prostate biopsy. (A) H&E staining of the biopsy with the single small focus of acinar adenocarcinoma (5×); (B) immunohistochemistry shows loss of basal cells and positive reaction for p504s in the tumor cells (p504s/p63 double staining, 5×); (C) few cells showing immunohistochemical membranous CD56 positivity. Nevertheless, they show the characteristic morphology of neuroendocrine cancer cells (CD56, 40×); (D) the typically high proliferation of the tumor cells with neuroendocrine morphology is demonstrated with immunohistochemistry (Ki67, 10×); (E) biopsy with the carcinoma showing neuroendocrine morphology (H&E, 5×); (F) magnified version of *Figure 1E* showing tumor area with neuroendocrine morphology. The nuclei show finely granular chromatin, high nuclear-to-cytoplasmic ratio, inconspicuous nucleoli and nuclear molding. The tumor grows in solid sheets. The arrows point at multiple mitotic figures, the arrowheads point at tumor necrosis with apoptotic bodies (H&E, 40×). H&E, hematoxylin eosin.

as well as a PET-CT with both FDG and PSMA tracers. The findings have revealed a 5 cm × 3.5 cm local tumor mass with retroperitoneal lymph node metastases, bone metastases such as vertebral, pelvic and costal, and a lung lesion of 1.4 cm at the left lower lobe (*Figure 2A* on the left shows FDG PET-CT at diagnosis and *Figure 2B* on the left shows PSMA PET-CT at diagnosis). Based on the clinical staging of prostate cancer using tumor, node and metastasis (TNM) system, the patient had a clinical stage T3cN1M1.

Based on a multidisciplinary team discussion between urologists and oncologists, a carboplatin (AUC 5 at day 1) and etoposide (100 mg/m^2/over three days)-based chemotherapy every 4 weeks for 6 cycles, as well as androgen deprivation therapy (ADT) using an luteinizing hormone-releasing hormone (LHRH) antagonist, were initiated. Carboplatin has been chosen as an agent due to deteriorated renal function at presentation with creatinine levels of 1.19 mg/dL and glomerular filtration rate of 49 mL/min/1.73 m^2. Moreover, due to ECOG 3 status at presentation, carboplatin was chosen to reduce the toxicity of the treatment. Due to extended bone metastases, additional therapy with denosumab 120 mg/4 weekly although metastatic hormone sensitive stage of disease has been started.

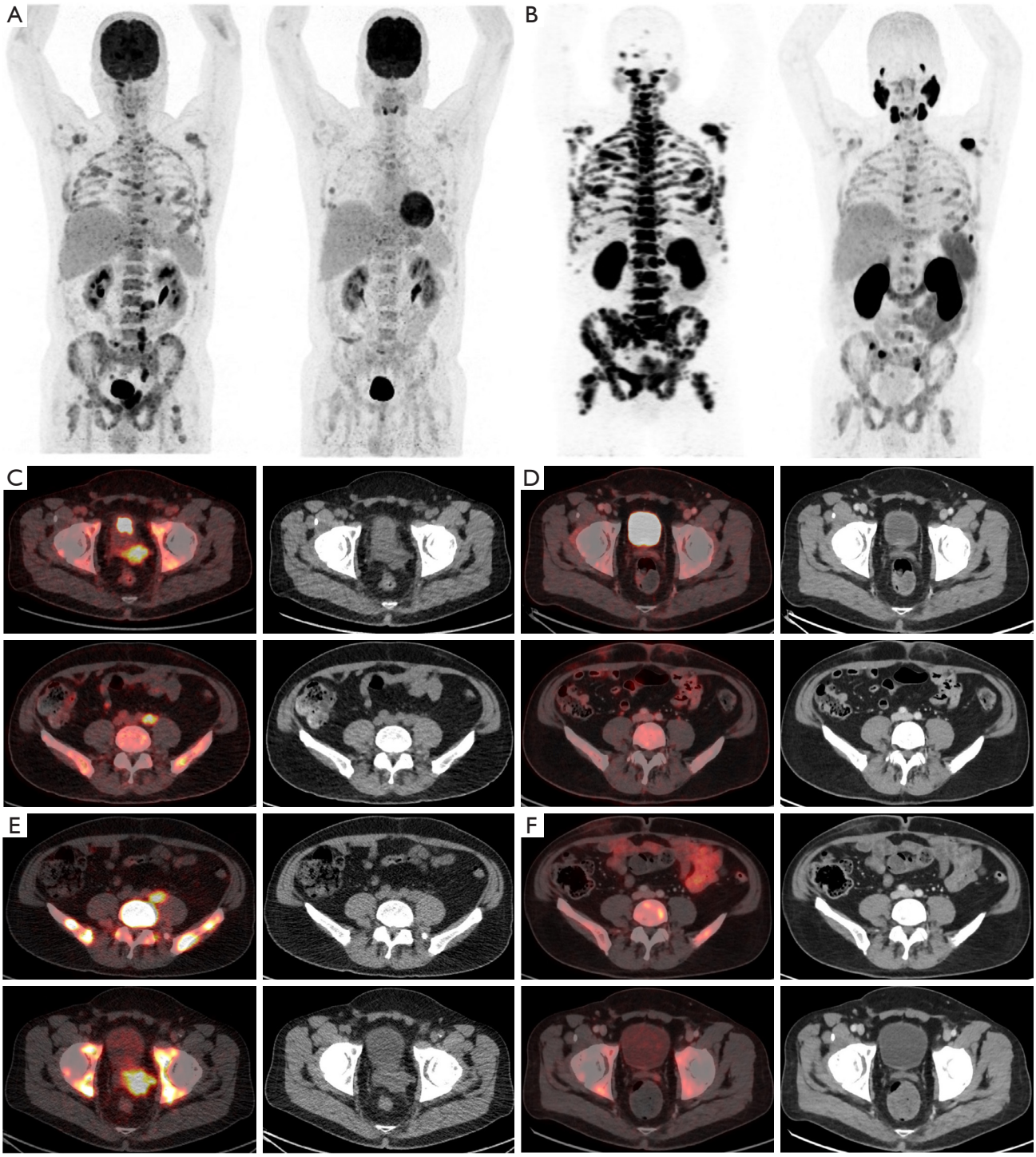

Figure 2 Imaging results at diagnosis and through the course of treatment. FDG PET-CT (A) and PSMA PET-CT (B) whole-body scans showing the comparison of the metabolically active metastases before (on the left) and after 6 cycles of chemotherapy with an addition of GnRH antagonist (on the right). FDG PET-CT (C,D) and PSMA PET-CT (E,F) scans with concomitant CT scans: at the diagnosis (C,E) and re-staging after 6 cycles of chemotherapy with etoposide/carboplatin with an addition of GnRH antagonist (D,F). FDG PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; PSMA, prostate-specific membrane antigen; GnRH, gonadotrophin-releasing hormone.

Remarkably, after the first chemotherapy cycle the performance status of the patient dramatically improved from ECOG 3, caused by pain the patient experienced from an extensive metastatic load and chronic inflammation due to pro-inflammatory cytokines, to ECOG 0. Before starting the chemotherapy, the patients pain medication included tramadol 100 mg and additionally metamizole 500 mg up to 3 times daily. After the first chemotherapy cycle, the pain medication dosage was bisected and after the second cycle the patient was pain free and all the pain medication was discontinued. To assess the urinary symptoms, The International Prostate Symptom Score (IPSS) was used. At presentation the patient had a score of 16 which has improved to 5 after finishing the chemotherapy. After the third cycle of chemotherapy, the LDH levels decreased to 260 U/L (normal range, 135–225 U/L) and PSA levels to 0.42 ng/mL. Surprisingly Chromogranin A levels went up to 248 µg/L (normal range <102 µg/L), but after the last cycle of chemotherapy decreased to 61.1 µg/L. LDH levels after the sixth cycle of chemotherapy went down to 256 U/L and PSA levels remained stable. As CEA and CA-19 were negative at diagnosis, these parameters have been further controlled after the sixth cycle of the chemotherapy and remained at normal range (CA-19 <9 kU/L and CEA <1.8 µg/L). Re-staging using PSMA PET-CT after three cycles of chemotherapy showed impressive metabolic response with no PSMA active lymphatic metastases and regredient bone metastases, consistent with PSA level decreasing to 0.3 ng/mL. By the end of the 6th chemotherapy cycle in March 2023, we have performed imaging using both FDG PET-CT and PSMA PET-CT, which have demonstrated no sign of increased glucose metabolism and overall a picture of a significant treatment response (*Figure 2C,2D* for FDG PET-CT and *Figure 2E,2F* for PSMA PET-CT).

Currently, the patient is pain free without any pain medication with an ECOG performance status of 0. A multidisciplinary team discussion was hold after the patient has finished the chemotherapy on further treatment. The apalutamide has been chosen as it didn't have interactions with patient's long-term medication, didn't require the addition of cortisone with its side effects (abiraterone), didn't have fatigue as a side effect (enzalutamide) as patient wanted to regain an active lifestyle he had before his illness. Since June 2023 apalutamide 240 mg/d has been added to ADT with no side effects.

Additionally, somatic testing of 523 genes of the primary tumor has been performed using TruSight Oncology. It revealed copy number loss in *BRCA2* (1 copy), *RB1* c.2247_2259del13 (p.Y749*) AF29%. Microsatellite instability (MSI) testing shown to be stable. Germline testing for the copy number loss in *BRCA2* was performed and was unremarkable, confirming that this copy number variant is a somatic mutation. Germline testing for the *RB1* mutation was not performed because of allele frequency (suggesting somatic origin), lack of history of retinoblastoma and *RB1* mutations being frequently found in prostate carcinoma. In line with these finding, in case of progression, the therapy with poly(ADP-ribose) polymerase inhibitor (PARPi) olaparib would be initiated.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Generally, neuroendocrine cells are physiological components of prostatic tissue, that comprise no more than 1% of total epithelial population and are scattered among basal and luminal cells (6). Their function remains unclear, they have been shown to secrete biogenic amines, neuropeptides and cytokines. They also play role in growth and differentiation of a prostate gland (7). These cells do not express androgen receptors (AR) and are resistant to hormonal therapy that targets AR signaling (8).

The terminology used to describe NEPC has varied in literature. Until 2016, the World Health Organization divided prostatic neuroendocrine tumors into five groups: standard adenocarcinoma with neuroendocrine (NE) differentiation, adenocarcinoma with Paneth cell-like NE differentiation, carcinoid tumor, SCNC and large cell NE carcinoma (9). Of note, carcinoid tumor and large cell NE carcinoma are so rare, that the most of the so-called NE tumors of the prostate are SCNCs—pure SCNCs or mixed with conventional adenocarcinoma (10). The most common serum markers for neuroendocrine tumors are chromogranin A, CD 56, synaptophysin and neuron-specific enolase (11). Of importance, elevated expression levels of chromogranin A have been described to be associated with higher disease burden and poorer prognosis in patients with prostate cancer (12). NEPC is characterized by its aggressive course of the disease, lack of response to

hormonal therapies and poor prognosis (2).

Since the combination of cisplatin and etoposide was proved to be an effective treatment for small cell lung cancer (SCLC), the same regiment was studied for poor differentiated NEPC, becoming the most used treatment due to morphological similarities of these tumors (13). The addition of doxorubicin to the schema didn't prove any clinical benefit for the patients with NEPC (14). *Table 1* summarizes some published case reports of *de novo* NEPC, including patient and tumor characteristics, treatment and outcome.

Treatment options for SCNC, using novel targeted therapy, that originate from the results of conducted clinical studies or published case reports, are depicted sparely in *Table 2*.

For example, it has been recently reported, that treatment with the anti-programmed cell death protein 1 (PD-1) antibody pembrolizumab in the case of a patient with high MSI resulted in completed response [follow-up (FU) time 14 months] (26). Promising results have originated from a phase III study for patients with SCLC, treated with an addition of the anti-PDL1 antibody atezolizumab to standard chemotherapy with carboplatin and etoposide (32). Unfortunately, the same combination for the patients with SCNC didn't show any benefit from the addition of immunotherapy [median progression-free survival (PFS) 3.4 months and OS of 8.4 months] (27).

Defects in homologous recombination repair (HRR) genes such as *BRCA1* and *BRCA2* have been detected in patients with advanced prostate cancer and are associated with worse outcome (33). Germline mutations in *BRCA1/2* predict response to platinum-based chemotherapy and PARPi. That is why the combination of chemotherapy and maintenance with PARPi has become a standard of care of pancreatic or breast cancers with *BRCA1/2* mutations (34,35). With prostate cancer, there are no clinical studies on maintenance therapy with PARPi for NEPC, therefore case reports are important for making treatment decisions until clinical trial data emerges.

Considering the difference between *de novo* SCNC and treatment-related SCNC (t-SCNC), the work of Aggarwal *et al.*, that was mentioned previously, looked closely into genomic characteristics of t-SCNC. Twelve patients (4 with mixed t-SCNC and 8 with pure t-SCNC) were included in somatic targeted genomic sequencing. Variants predicted to lead to loss of function in *TP53* and/or *RB1* were found in 10 of 12 patients with t-SCNC. None of the 12 patients had alterations in *BRCA1* or *BRCA2* genes (3). In our case, the patient had copy number loss in *BRCA2* gene, which can be related to differences in treatment and response in patient with *de novo* SCNC in comparison to t-SCNC. The case report published by Pandya *et al.*, highlights a case of t-SCNC in patient with *BRCA2* mutation, that had initially good response to platinum-based therapy, but developed a *BRCA2* somatic reversion mutation during maintenance therapy with PARPi within 6 months (28). Therefore, clinical studies are needed to estimate the prevalence of *BRCA* alterations in SCNC to establish more effective treatment strategies.

Some aggressive variants of prostate cancer showed similar molecular features with SCNC such as combined alterations in tumor suppressors such *RB1 Tp53*, and/or phosphatase and tensin homolog (*PTEN*), which is likely indicating shared underlining biology (36). Loss of the *PTEN* is one of the most common aberrations in prostate cancer, associated with poor prognosis and worse response to abiraterone treatment (37-39). *PTEN* inactivation leads to increased cell survival and proliferation because of hyperactivation of phosphatidylinositol 3-kinase *(PI3K)-Akt*-mammalian target of rapamycin (*mTOR*) pathway (40). In a case report of a heavily pretreated patient with mCRPC, who had *PTEN* inactivating mutation, everolimus, a *PI3K-Akt-mTOR* pathway inhibitor, was used and the patient was able to reach stable disease (29).

Novel imaging techniques are promising tools for detection and treatment of neuroendocrine tumors. Such radionuclide therapies as lutetium-177 (^{177}Lu)-PSMA and^{177}Lu-DOTATATE showed not only promising results in advanced midgut neuroendocrine tumors (41), but also in patient with mCRPC with neuroendocrine differentiation, who first received 4 cycles of ^{177}Lu-PSMA, followed by ^{177}Lu-DOTATATE treatment (30). Thought the efficacy of the ^{177}Lu-DOTATATE treatment may be linked to the degree of ki-67 proliferation index and is more effective for the patients with index ≤55% (42).

Emerging agents that target signaling pathways in cancer cells have been implicated in NE tumor differentiation and progression and are being investigated with emerging promising data. For example, a significant overexpression and gene amplifications of the genes aurora kinase A (*AURKA*) and N-myc (being 40%) has been linked to neuroendocrine differentiation of prostate cancer that can be targeted with AURKA-inhibitor in preclinical trials (43). Although in a phase 2 clinical AURKA-inhibitor alisertib did not meet the primary endpoint of 6-month radiologic PFS,

Table 1 Characteristic of reported cases on *de novo* SCNC

Case	Author	Age, years	PSA (ng/mL)	Pathology (pure/mixed)	Synaptophysin/chromogranin A/CD56	Main symptom	Biopsy type	Metastasis at diagnosis	Treatment	Outcome
1	Bhandari *et al.* [2020] (15)	63	9.41	NA	+/NA/NA	Urinary retention Renal failure	Prostate Biopsy	Yes (lymph nodes, bones)	Carbo + eto	Death after 3 months from diagnosis. Only one cycle was applied
2	Teh *et al.* [2022] (16)	52	0.8	NA	+/–/–	Hematuria Perineal pain	Prostate biopsy	No	Cis + eto RT	Alive after 4 cycles. Ongoing RT
3	Pokhrel *et al.* [2022] (17)	65	9.81	Mixed	+/+/+	Urinary retention Acute kidney injury	Prostate biopsy	Yes (bone)	IC Enza + ADT RT of spine metastasis Durvalumab + cabazitaxel	Discontinue of the treatment due to side effects. Patient died couple of days after
4	Demirtaş *et al.* [2013] (18)	60	47.50	NA	NA/+/+	LUTS	Prostate biopsy	No	Surgery: bilateral orchiectomy TURP RT for metastasis	Death 6 months after surgery
5	Rauf *et al.* [2020] (19)	61	139	Mixed	+/NA/+	Left side neck swelling	Biopsy of cervical lymph nodes	Yes (bones, lymph nodes)	Cis + eto ADT	NA
6	Riaza Montes *et al.* [2021] (20)	65	2.45	NA	+/–/+	Edema Hypertension Paraneoplastic syndrome	Prostate biopsy	Yes (visceral)	NA	Died 20 days after admission to the hospital
8	Dixit *et al.* [2012] (21)	66	4.8	NA	NA	Intermittent constipation and diarrhea	Prostate biopsy	Yes (lymph nodes)	ADT Carbo + eto RT Docetaxel	Died 9 month after diagnosis
9	Wei *et al.* [2016] (22)	78	33	Mixed	+/+/NA	Frequent urination	Prostate biopsy	Yes (bone)	ADT for 12 months Carbo + eto	Death 18 month after diagnosis
10	Negulescu *et al.* [2022] (23)	67	Elevated	NA	+/+/+	Pelvic pain	Prostate biopsy	Yes (liver, lymph nodes, bone)	Cis + eto	Developed multiple brain metastases 6 months post treatment
11	Hingorani *et al.* [2014] (24)	53	119	Mixed	+/NA/+	Acute kidney injury	Prostate biopsy	Yes (bone, lymph nodes, lung)	ADT Cis + eto	NA
12	Hasken *et al.* [2023] (25)	81	0.62	NA	+/–/NA	Left flank pain LUTS	Prostate biopsy	Yes (penile, lymph nodes, lung, bone)	Carbo + eto Nivolumab	Died 9 month after diagnosis
13	Our case	60	7.9	Mixed	–/–/+	Abdominal pain	Prostate biopsy	Yes (bone, lymph nodes, lung)	ADT Carbo + eto	Alive, ongoing ADT + apalutamide

SCNC, small cell neuroendocrine prostate cancer; PSA, prostate-specific antigen; NA, not applicable; carbo + eto, carboplatin + etoposide; cis + eto, cisplatin + etoposide; RT, radiotherapy; IC, irinotecan + carboplatin; enza, enzalutamide; ADT, androgen deprivation therapy; LUTS, low urinary tract symptoms; TURP, transurethral prostate resection.

Table 2 Overview of novel therapies used for t-SCNC

Case/ trial	Prostate cancer type	Genetic testing findings	Prior treatment	Agent used	Results
Yoshida *et al.* (26)	t-SCNC	MSI	Carbo + eto Radiation 70 Gy Irinotecan (2 cycles)	Pembrolizumab	CR (follow-up time of 14 months)
Wee *et al.* (27)	t-SCNC, *de novo* SCNC	NA	None ADT Docetaxel Cabazitaxel Carbo + eto	Atezolizumab Carbo + eto	No benefit (median PFS of 3.4 months, median OS of 8.4 months)
Pandya *et al.* (28)	t-SCNC	*BRCA2*	ADT + abiraterone Cis + eto	Olaparib Pembrolizumab	No benefit, patient died 18 months after t-SCNC diagnoses
Kmak *et al.* (29)	CRPC	*PTEN* inactivation	ADT Docetaxel Abiraterone Cabazitaxel	Everolimus	Stable disease, discontinued after 8 months due to fatigue
Assadi *et al.* (30)	t-SCNC	NA	ADT	4 cycles of ^{177}Lu-PSMA, followed by ^{177}Lu-DOTATATE	Alive
Beltran *et al.* (31)	SCNC patients with elevated neuroendocrine markers	*RB1* (55%), *TP53* (46%), *PTEN* (29%), *BRCA2* (29%), *AR* (27%)	Abiraterone or enzalutamide: 40% Docetaxel: 32% Platinum chemotherapy: 58%	Alisertib 50 mg twice daily for 7 days every 21 days	Median OS was 9.5 months (95% CI: 7.3–13)

t-SCNC, treatment-related small cell neuroendocrine cancer; MSI, microsatellite instability; Carbo + eto, carboplatin + etoposide; CR, complete response; NA, not applicable; ADT, androgen deprivation therapy; PFS, progression-free survival; OS, overall survival; *BRCA2*, breast cancer gene 2; Cis + eto, cisplatin + etoposide; PSMA, prostate-specific membrane antigen; CRPC, castration resistant prostate cancer; *RB1*, retinoblastoma gene; *PTEN*, phosphatase and tensin homolog; AR, androgen receptors; CI, confidence interval.

four exceptional responders were identified with an PFS of 3.8 years (31).

Conclusions

SCNC is rare and aggressive type of cancer, which progresses rapidly. Currently there is no standard of treatment and the protocol for a SCLC using chemotherapy with etoposide and platinum-based agents is used (44). Despite initial response, this standard of care fails to improve the outcome of these patients. As most of the cases are diagnosed in the advanced stages, the prognosis is poor and new therapy options are desperately needed.

We present a case of *de novo* SCNC mixed with adenocarcinoma, elevated PSA levels at diagnosis, mimicking the symptoms of prostatitis. At the diagnosis the patient had lymph node, bone and lung metastases. He underwent 6 cycles of chemotherapy with carboplatin and etoposide combination and ADT for the adenocarcinoma component. After chemotherapy, the imaging results showed no sign of metabolic expression and overall the picture of impressive treatment response. Currently the patient is alive and well under the treatment with ADT and apalutamide. In addition, we provide an overview on current and emerging treatment options for this rare disease.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-541/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-541/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Aggarwal R, Zhang T, Small EJ, et al. Neuroendocrine prostate cancer: subtypes, biology, and clinical outcomes. J Natl Compr Canc Netw 2014;12:719-26.
3. Aggarwal R, Huang J, Alumkal JJ, et al. Clinical and Genomic Characterization of Treatment-Emergent Small-Cell Neuroendocrine Prostate Cancer: A Multi-institutional Prospective Study. J Clin Oncol 2018;36:2492-503.
4. Bakht MK, Derecichei I, Li Y, et al. Neuroendocrine differentiation of prostate cancer leads to PSMA suppression. Endocr Relat Cancer 2018;26:131-46.
5. Deorah S, Rao MB, Raman R, et al. Survival of patients with small cell carcinoma of the prostate during 1973-2003: a population-based study. BJU Int 2012;109:824-30.
6. Huang YH, Zhang YQ, Huang JT. Neuroendocrine cells of prostate cancer: biologic functions and molecular mechanisms. Asian J Androl 2019;21:291-5.
7. Xue Y, Smedts F, Verhofstad A, et al. Cell kinetics of prostate exocrine and neuroendocrine epithelium and their differential interrelationship: new perspectives. Prostate Suppl 1998;8:62-73.
8. Huang J, Yao JL, di Sant'Agnese PA, et al. Immunohistochemical characterization of neuroendocrine cells in prostate cancer. Prostate 2006;66:1399-406.
9. Humphrey PA, Moch H, Cubilla AL, et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. Eur Urol 2016;70:106-19.
10. Hu J, Han B, Huang J. Morphologic Spectrum of Neuroendocrine Tumors of the Prostate: An Updated Review. Arch Pathol Lab Med 2020;144:320-5.
11. Epstein JI, Amin MB, Beltran H, et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. Am J Surg Pathol 2014;38:756-67.
12. Guo Z, Wang Y, Xiang S, et al. Chromogranin A is a predictor of prognosis in patients with prostate cancer: a systematic review and meta-analysis. Cancer Manag Res 2019;11:2747-58.
13. Fjällskog ML, Granberg DP, Welin SL, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. Cancer 2001;92:1101-7.
14. Amato RJ, Logothetis CJ, Hallinan R, et al. Chemotherapy for small cell carcinoma of prostatic origin. J Urol 1992;147:935-7.
15. Bhandari R, Vengaloor Thomas T, Giri S, et al. Small Cell Carcinoma of the Prostate: A Case Report and Review of the Literature. Cureus 2020;12:e7074.
16. Teh S, Inn FX, Rizuana IH, et al. A rare case of prostate neuroendocrine tumor: A case report. Front Oncol 2022;12:1009146.
17. Pokhrel A, Nair K, Jaswani V, et al. Review of Checkpoint Inhibitor Immunotherapy in Neuroendocrine Tumor of

Prostate and Our Experience in 2 Cases. J Investig Med High Impact Case Rep 2022;10:23247096221093886.
18. Demirtaş A, Sahin N, Oztürk F, et al. Small cell prostate carcinoma: a case report and review of the literature. Case Rep Urol 2013;2013:387931.
19. Rauf A, Smith SF, Mukherjee R, et al. Not such a small diagnosis: small cell carcinoma of the prostate. J Surg Case Rep 2020;2020:rjaa117.
20. Riaza Montes M, Arredondo Calvo P, Gallego Sánchez JA. Small cell metastatic prostate cancer with ectopic adrenocorticotropic hormone hypersecretion: a case report. Ann Palliat Med 2021;10:12911-4.
21. Dixit S, Coup A, Hunt C, et al. Small cell cancer of the prostate. Urology 2012;80:e58-60.
22. Wei J, Zheng X, Li L, et al. Rapid progression of mixed neuroendocrine carcinoma-acinar adenocarcinoma of the prostate: A case report. Oncol Lett 2016;12:1019-22.
23. Negulescu MC, Mihai M, Gramaticu I. Neuroendocrine Carcinoma of the Prostate – a Case Report. J Med Radiat Oncol 2022;2:38-45.
24. Hingorani R, Young J, Alweis R. Mixed adenocarcinoma and neuroendocrine prostate cancer: a case report. J Community Hosp Intern Med Perspect 2014;4:25176.
25. Hasken W, Sun F, Mithqal A, et al. Primary Neuroendocrine Prostate Cancer with Penile Metastasis. Radiol Imaging Cancer 2023;5:e230013.
26. Yoshida T, Yaegashi H, Toriumi R, et al. Long response duration to pembrolizumab in metastatic, castration-resistant prostate cancer with microsatellite instability-high and neuroendocrine differentiation: A case report. Front Oncol 2022;12:912490.
27. Wee CE, Costello BA, Orme JJ, et al. Chemotherapy with atezolizumab for small cell or neuroendocrine carcinoma of the prostate: A single institution experience. Prostate 2021;81:938-43.
28. Pandya D, Shah M, Kaplan F, et al. Treatment-emergent neuroendocrine prostate cancer with a germline BRCA2 mutation: identification of a candidate reversion mutation associated with platinum/PARP-inhibitor resistance. Cold Spring Harb Mol Case Stud 2021;7:a005801.
29. Kmak JA, Agarwal N, He Y, et al. Exceptional Response to Everolimus in a Patient with Metastatic Castrate-Resistant Prostate Cancer Harboring a PTEN Inactivating Mutation. Case Rep Oncol 2020;13:456-61.
30. Assadi M, Pirayesh E, Rekabpour SJ, et al. 177Lu-PSMA and 177Lu-DOTATATE Therapy in a Patient With Metastatic Castration-Resistant Prostate Cancer and Neuroendocrine Differentiation. Clin Nucl Med 2019;44:978-80.
31. Beltran H, Oromendia C, Danila DC, et al. A Phase II Trial of the Aurora Kinase A Inhibitor Alisertib for Patients with Castration-resistant and Neuroendocrine Prostate Cancer: Efficacy and Biomarkers. Clin Cancer Res 2019;25:43-51.
32. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.
33. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748-57.
34. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017;377:523-33.
35. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med 2019;381:317-27.
36. Aparicio AM, Shen L, Tapia EL, et al. Combined Tumor Suppressor Defects Characterize Clinically Defined Aggressive Variant Prostate Cancers. Clin Cancer Res 2016;22:1520-30.
37. Cuzick J, Yang ZH, Fisher G, et al. Prognostic value of PTEN loss in men with conservatively managed localised prostate cancer. Br J Cancer 2013;108:2582-9.
38. Yoshimoto M, Cunha IW, Coudry RA, et al. FISH analysis of 107 prostate cancers shows that PTEN genomic deletion is associated with poor clinical outcome. Br J Cancer 2007;97:678-85.
39. Ferraldeschi R, Nava Rodrigues D, Riisnaes R, et al. PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. Eur Urol 2015;67:795-802.
40. Sun H, Lesche R, Li DM, et al. PTEN modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5,-trisphosphate and Akt/protein kinase B signaling pathway. Proc Natl Acad Sci U S A 1999;96:6199-204.
41. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017;376:125-35.
42. Zhang J, Kulkarni HR, Singh A, et al. Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients. J Nucl Med 2019;60:377-85.

43. Beltran H, Rickman DS, Park K, et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov 2011;1:487-95.

44. Papandreou CN, Daliani DD, Thall PF, et al. Results of a phase II study with doxorubicin, etoposide, and cisplatin in patients with fully characterized small-cell carcinoma of the prostate. J Clin Oncol 2002;20:3072-80.

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