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Case Report

Experience and Lessons Learned in the Treatment of Transforming Small Cell Neuroendocrine Carcinoma of the Prostate: A Case Report and Literature Review

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Abstract
Introduction: Small cell neuroendocrine carcinoma of the prostate (SCNECP) is a rare and highly malignant tumor that commonly transforms into conventional prostate adenocarcinoma (CPAC). Most of SCNECP cases cannot be detected and diagnosed early, and SCNECP is often diagnosed when there is liver and lung metastasis. Therefore, the early detection of the process from CPAC to SCNECP is crucial. ***Case Report:*** We present a case of a 73-year-old man who was initially admitted to our hospital with metastatic CPAC. He was administered goserelin acetate 3.6 mg combined with bicalutamide tablets (50 mg) once daily for endocrine therapy and docetaxel (100 mg) combined with prednisone (5 mg) twice a day. After treatment, the prostate-specific antigen (PSA) level decreased significantly, but the CEA, CA199, and CA125 levels began to increase progressively after a short decline. However, no solid tumor recurrence was observed in multiple reexaminations. It was not until 9 months after the elevation of tumor markers that multiple metastatic lesions appeared in the liver, which finally confirmed the diagnosis of metastatic SCNECP. After chemotherapy with etoposide 360 mg combined with carboplatin 200 mg, the tumor size was significantly reduced, and tumor markers decreased. However, the remission time was only 3 months. The patient's liver metastases continued to grow, and CEA, CA199, and CA125 levels continued to increase. ***Conclusion:*** During CPAC treatment, PSA levels continued to decrease, whereas CEA, CA199, and CA125 levels continued to increase. This suggests the possibility of the transformation of CPAC into SCNECP.

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Introduction

Small cell neuroendocrine carcinoma of the prostate (SCNECP) is a rare type of prostate tumor that is often derived from transformation after conventional prostate adenocarcinoma (CPAC) treatment [1]. This transformation may be related to the loss of tumor suppressor proteins such as PTEN, RB1, and TP53 [2]. It is generally believed that the transition from CPAC to SCNECP can occur through selective pressure of potent AR-targeting agents in the absence of TP53/RB1 loss [3]. However, this transition process should be considered a complex process of tumor evolution. One study suggested that the disease continuum from CPAC to SCNECP should be divided into the following five categories: CPAC (adenocarcinoma with androgen receptor (AR) and prostate-specific antigen [PSA]), AR-low CPAC (weak AR and PSA, negative for neuroendocrine [NE] markers), bisexual CPAC (co-expressing AR, PSA, and NE markers), double negative CPAC (negative for AR, PSA, and NE/small cell carcinoma [SC] markers), and NE/SC [4]. SCNECP does not necessarily express PSA. Therefore, PSA levels did not reflect SCNECP transformation. Therefore, the conversion of CPAC to SCNECP was difficult to detect. It is vital to find relevant evidence for the advance transformation of CPAC into SCNECP. Our case showed that decreased PSA and increased CEA, CA199, and CA125 levels may predict the transformation of CPAC to SCNECP. This has crucial implications for the early detection and treatment of transformed SCs of the prostate.

Case Presentation

A 72-year-old male patient was admitted to the hospital because of left cervical lymph node enlargement for 1 month on July 1, 2022. Subsequently, fluorodeoxyglucose positron emission tomography/computed tomography (CT) was performed: enlarged lymph nodes in the left posterior cervical triangle, the supraclavicular region, the right lower paratracheal, the subaortic arch, the bilateral hilar lung, the retroperitoneal para-abdominal aorta, and the bilateral iliac vessels showed increased FDG metabolism and systemic bone destruction accompanied by increased FDG metabolism. Prostate cancer (PC) with lymph node and bone metastases was considered. Visceral metastases were not observed (Fig. 1). The main symptom of the patient was the enlargement of multiple lymph nodes, and the pain caused by bone metastasis was not obvious. Prostate biopsy revealed PC. The Gleason score was 4 + 5. Immunohistochemistry (IHC): CK7 (−), CK20 (−), EMA (−), Ki-67 (+,70%), PSA (+), and P504 s (+). He was administered goserelin acetate 3.6 mg combined with bicalutamide tablets (50 mg) once daily and docetaxel 100 mg combined with prednisone 5 mg twice a day, chemotherapy every 21 days. At the same time, zoledronic acid inhibits bone destruction. The PSA levels of the patients decreased gradually, from the highest 2,247.6 ng/mL to the lowest 8.78 ng/mL. CEA decreased from 103.88 ng/mL to 23.92 ng/mL, CA199 decreased from 77.6 Ug/mL to 39.4 Ug/mL, and CA125 levels decreased from 63.0 Ug/mL to 32.1 Ug/mL. However, PSA levels decreased for 7 months, whereas CEA, CA199, and CA125 levels began to increase after 3 months (Fig. 2). We also considered a second primary tumor or disease progression. However, no evidence of tumor progression or metastasis was detected by gastroenteroscopy or routine contrast-enhanced CT performed every 2 months. Therefore, the chemotherapy regimen was not changed until metastasis was considered in June 2023. Chest and abdominal CT showed diffuse multiple space-occupying lesions in the liver parenchyma. Needle biopsy of the liver tumor showed small cell neuroendocrine carcinoma (SCNEC) in the liver tissue on June 21, 2023. IHC: CD56 (+), CK19 (+). CDX-2 (−), CgA (+), Gly-3 (+), Hepa (−), Ki-67 (+90%), NSE (+), PSA (−), Syn (+), INSM1 (+), TTF-1 (−) (shown in Fig. 3). Considering the poor appetite due to liver metastasis, a reduced dose EP regimen (etoposide

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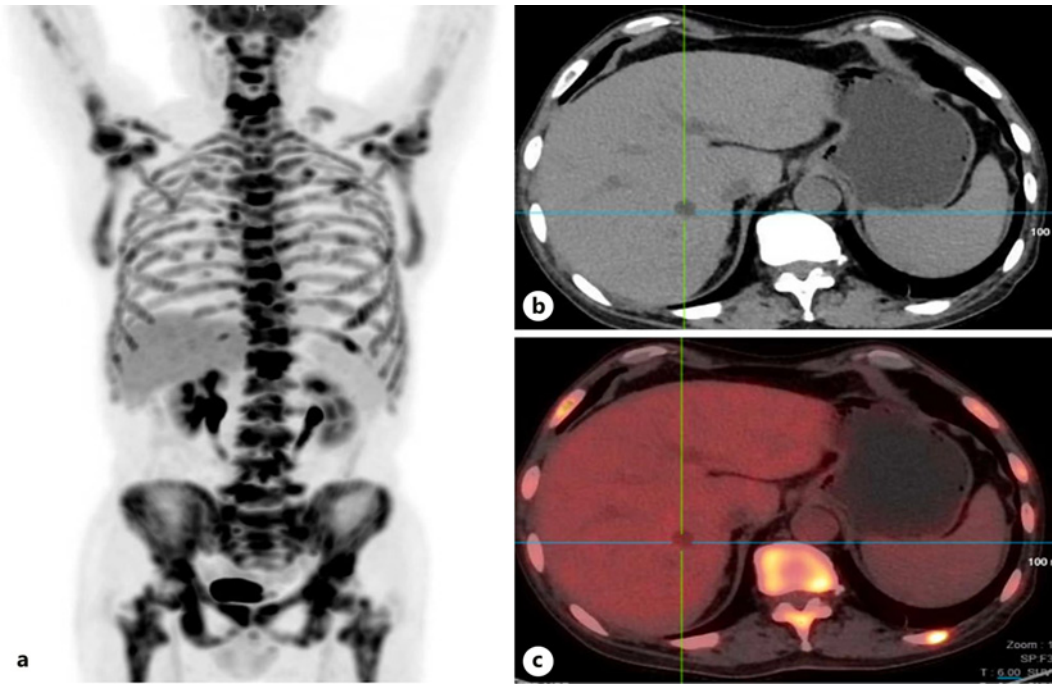

Fig. 1. Positron emission tomography/CT showed multiple bone metastases of PC (**a**) and CT showed hepatic cysts in the liver (**b**), there were no metastases in the liver (**c**).

360 mg combined with carboplatin 200 mg) was administered for three cycles. Re-examination of CT on August 16, 2023, showed that the liver metastasis was significantly smaller than before. However, after only 3 months of remission, a reexamination of CT on September 11, 2023, showed that the liver metastasis had increased (Fig. 4). The patient's family declined further chemotherapy, and he died on November 15, 2023 (Fig. 5).

Discussion

Most cases of SCNECP cannot be detected and diagnosed early, and SCNECP is often diagnosed when liver and lung metastases are present. Therefore, the early detection of the process from CPAC to SCNECP is crucial. However, we failed to detect and diagnose SCNECP early and waited until the patient had multiple liver metastases before initiating treatment, which significantly delayed the treatment. During the transformation from CPAC to SCNECP, CPAC can benefit from chemotherapy and endocrine castration, which results in a continuous decrease in PSA levels. However, after the transformation from CPAC to SCNECP, the transformed SCNEC often cannot benefit from docetaxel 100 mg combined with prednisone 5 mg twice a day, chemotherapy, and endocrine castration. Therefore, it leads to a decrease in PSA levels and an increase in CEA, CA125, and CA199 levels. In other words, if such phenomena occur, a high probability indicates that the CPAC has begun to transform into the SCNECP. This finding allowed us to detect SCNECP transformation earlier, which has important clinical significance, especially in patients with localized PC. Early detection of SCNEC transformation can lead to local radical radiotherapy and chemotherapy [5, 6], rather than waiting for visceral metastasis before treatment. In this patient, we failed to identify the tumor in a timely manner in the presence of persistently elevated tumor markers, and a liver biopsy was not performed until the patient presented with multiple liver metastases.

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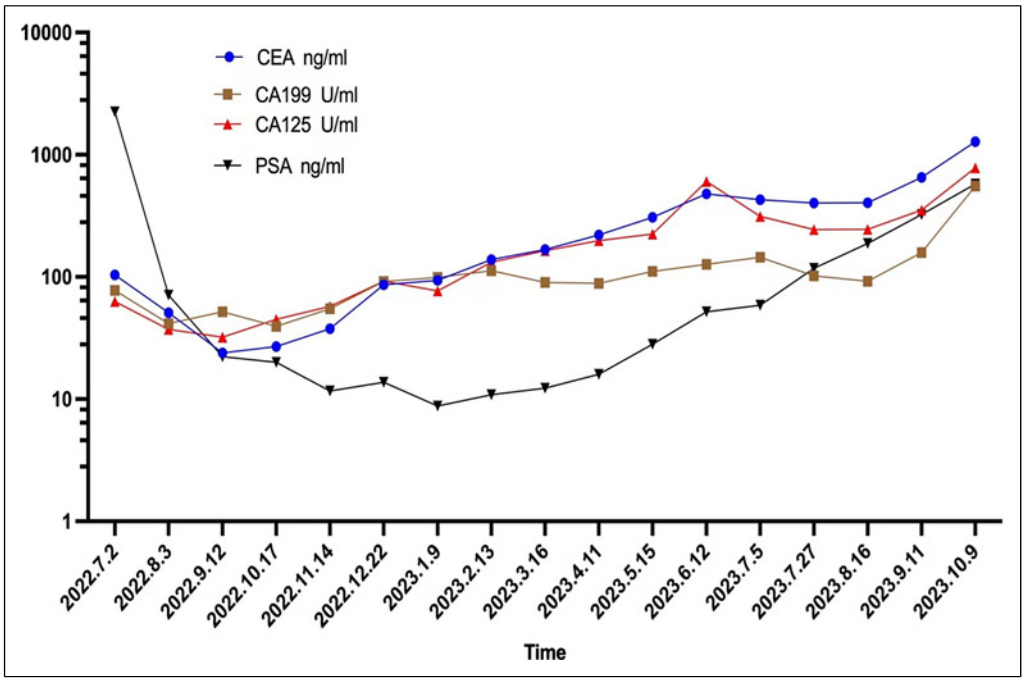

Fig. 2. Trend graph of tumor markers.

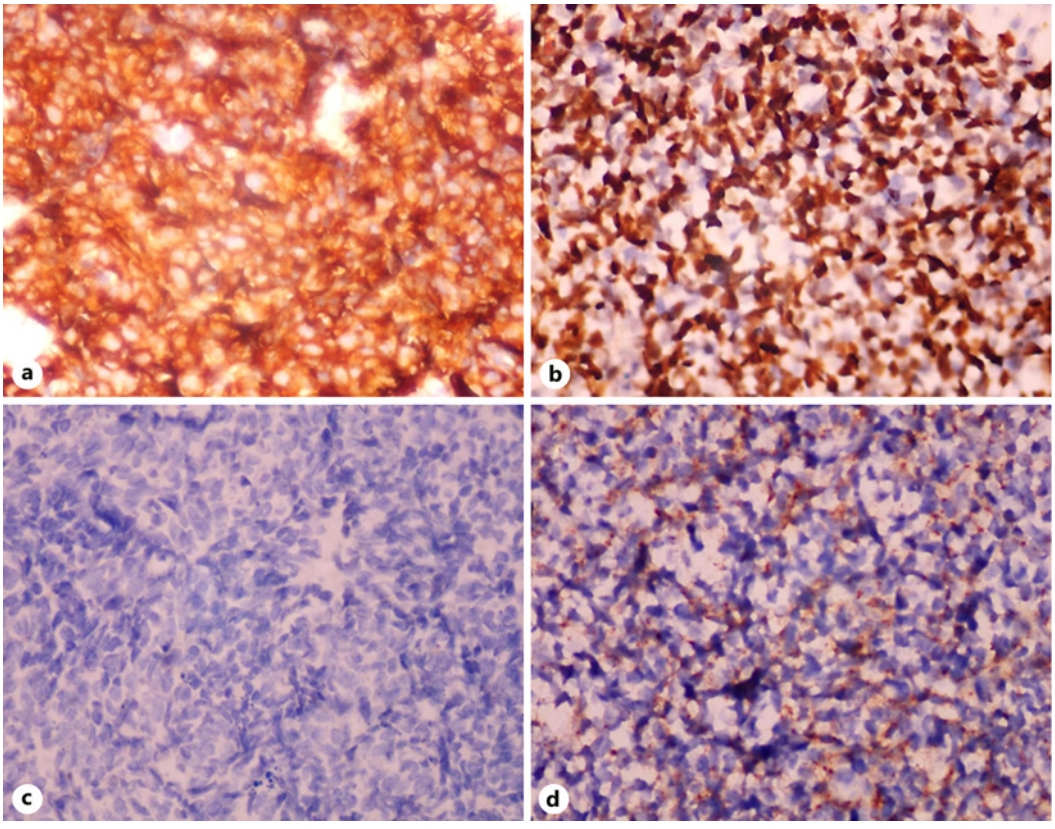

Fig. 3. IHC. **a** Syn positive [×400]. **b** Insulinoma-associated protein 1(INSM1) positive [×400]. **c** PSA negative [×400]. **d** NSE positive [×400].

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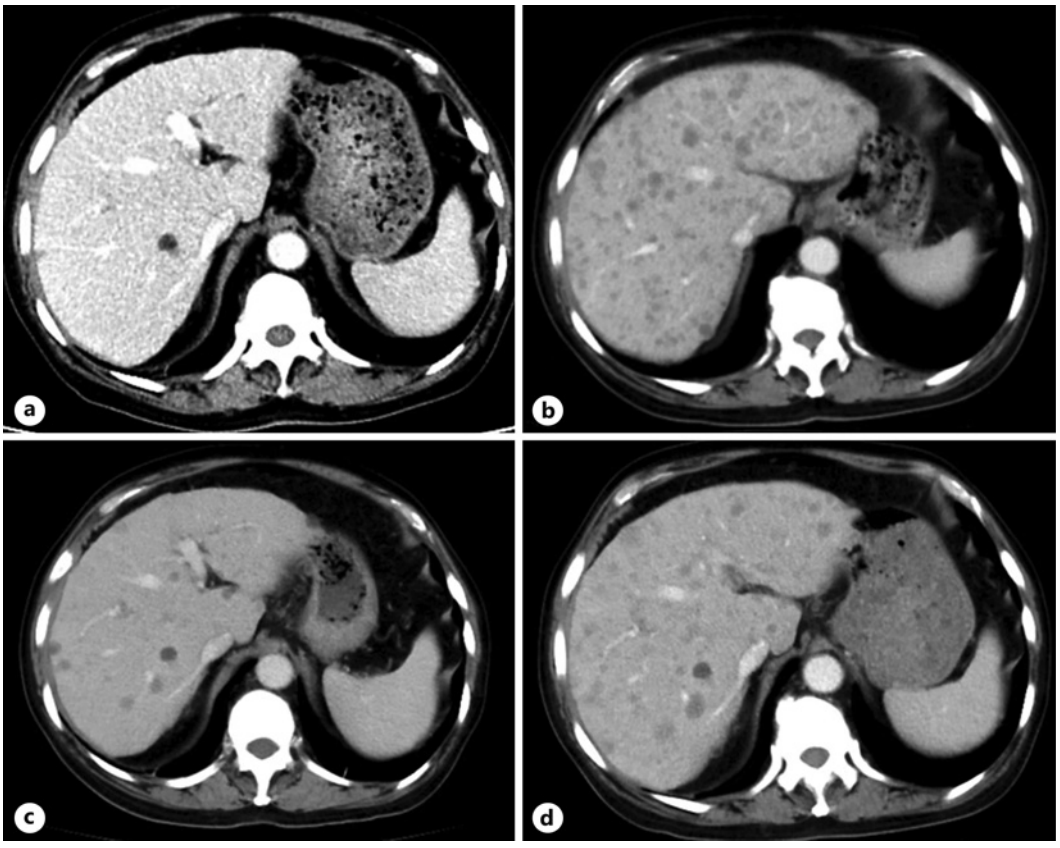

Fig. 4. a On April 13, 2023, CT showed no metastasis of hepatic cysts. **b** On June 13, 2023, after the continuous increase of CEA, CA199, and CA125 for 9 months, CT showed diffuse multiple metastases in the liver. **c** After 3 cycles of etoposide combined with carboplatin chemotherapy, CT reexamination on August 17, 2023, showed that liver metastases were significantly reduced. **d** Reexamination of CT on September 12, 2023, showed that the liver metastasis increased again and the disease progressed.

Therefore, the opportunity for early treatment was missed. Clearly, we have overlooked the importance of a repeat prostate biopsy. If this patient had undergone a second prostate biopsy after the elevation of tumor markers, the conversion of CPAC to SCNECP might have been detected earlier. This was a very profound lesson.

SCNECP is a rare type of PC. The majority of SCNECP are derived from conversion after CPAC treatment. The possibility that a subset of CPAC may progress to SCNECP has been established in preclinical models and case reports [1, 7]. The LTL331 model accurately summarized the clinical course of patients with an LTL331 source. LTL331 (adenocarcinoma) takes 6–8 months after castration to become LTL331R (SCNEC) [8]. This result was consistent with the findings of the present study. However, the transformation from CPAC to SCNECP is a dynamic process, and the patient may still have adenocarcinoma components after the transformation. Therefore, the patient may have two tumor cells simultaneously during the course of the disease [9].

Compared with CPAC, SCNECP is more malignant and is characterized by low serum PSA, high serum NE markers, multiple visceral metastases, and poor response to chemotherapy drugs [10]. SCNECP should be suspected if the patient shows rapid disease progression during CPAC treatment [11]. The liver is the most common site for SCNECP. Studies have shown that patients with liver involvement due to metastatic SCNECP have poor prognosis [1, 12]. IHC is the most important diagnostic tool for SCNECP. Almost all SCNECP may be positive for one or more NE markers (synaptophysin, chromogranin, and neuron-specific enolase) [9]. Therefore, it

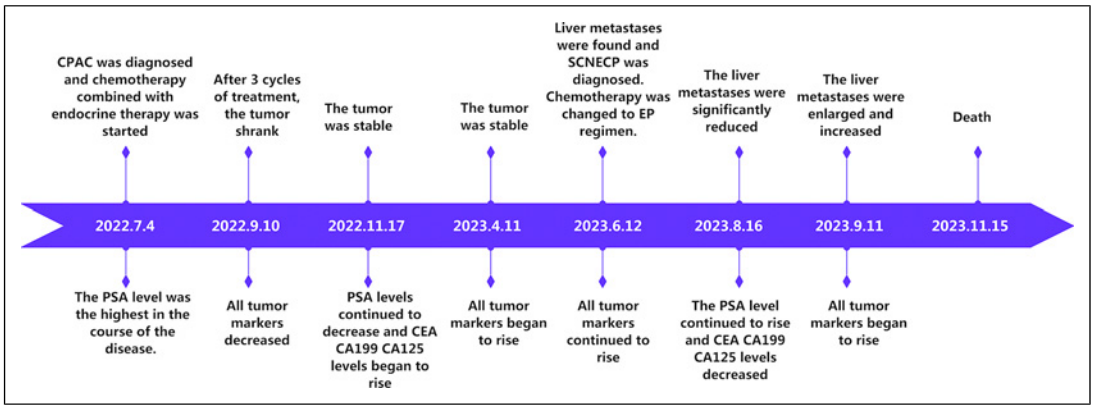

Fig. 5. Timeline summarizing the main events of this case report.

is not difficult to diagnose SCNEC. However, it is difficult to distinguish the origin of SCNEC using IHC alone. It is essential to distinguish the primary sites of SCNEC (mainly the prostate and lungs) for patient management. However, TTF-1 was expressed in both lung cancer and SCNECP. PSA, or AR. Although PSA and AR are supportive of a prostatic origin [4, 13], PSA and AR expression are frequently lost in SCNECP [14]. Therefore, the diagnosis of SCNECP requires comprehensive consideration of clinical manifestations and medical history. In the present case, the patient had no definite lung tumor; therefore, SCNEC was considered to have transformed from CPAC. Once SCNECP is diagnosed, patient survival time is very short. One study found that patients with SCNECP liver metastases had a median survival of only 4 months [15].

PSA is widely used in clinical practice as an important prognostic and predictive marker of PC [16]. In general, CPAC-related tumor marker elevation is mainly PSA, and other tumor markers are rarely increased [17]. However, elevations in markers such as CEA, CA125, and CA199 most likely indicate the presence of metastasis to visceral sites, such as the lung or liver [18, 19]. Alternatively, conversion of CPAC to SCNECP occurred. Several studies have shown that SC of the prostate can lead to the elevation of a variety of tumor markers such as CEA, CA125, and CA199 [20].

The serum NSE is a critical SC-associated tumor marker that we did not test when we initially diagnosed CPAC because it is not necessary in the diagnosis and treatment of CPAC. When SCNECP was diagnosed, the serum NSE levels were measured. On July 27, 2023, the patient's serum NSE was 105.8 ng/mL. After two cycles of chemotherapy, the serum NSE decreased to 39.68 ng/mL. At the same time, the liver metastases were significantly reduced; therefore, serum NSE can reflect the efficacy of chemotherapy. Obviously, if serum NSE can be monitored early, it can better indicate whether conversion from CPAC to SCNECP has occurred. This is noteworthy in the treatment of CPAC.

Treatment differs between advanced CPAC and SCNECP. Although both originate from the prostate, CPCA can benefit significantly from docetaxel combined with androgen deprivation therapy. In addition, most CPCA are accompanied with bone metastases. Emerging evidence suggests that the combination of bone-targeted agents with abiraterone acetate, enzalutamide and radium-223 can improve clinical efficacy and prolong the survival of patients with CRPC with bone metastases [21]. However, there is currently no standard treatment for SCNECP. Etoposide combined with cisplatin or carboplatin is the most commonly used treatment for SCNECP [22]. However, most patients do not have progression-free survival (PFS) after 4 months of chemotherapy. One study showed that the median overall survival of SCNECP patients was only 10 months [23], and most patients die within 1 year of diagnosis. Few studies have investigated radiotherapy in the treatment of SCNECP. Two studies have shown

that radiotherapy is effective for the treatment of limited-stage SCNECP and can achieve complete remission [5]. However, randomized controlled trials on radiotherapy for limited-stage SCNECP are lacking. In addition, the correct identification of the site of origin of metastatic SCNEC is vital for patient prognosis and treatment. The treatment of SCNECP differs from that of primary lung SCNEC. Lung SCNEC can be treated with chemotherapy combined with immunotherapy such as atezolizumab [24] or durvalumab [25]. In contrast, available data suggest that SCNECP does not benefit from immunotherapy. One study showed that in patients with advanced SCNECP who received first-line chemotherapy combined with immunotherapy (atezolizumab), the median PFS was 3.4 months and the median overall survival was 8.4 months [26]. However, the sample size of patients with SCNECP is small, and there is a lack of randomized controlled trials on immunotherapy for SCNECP. There are several reasons for the poor efficacy of immunotherapy, which may be related to the expression of PD-L1. In addition, dysbiosis of the gut microbiota may lead to poor immunotherapy efficacy [27]. In addition, the ECOG score of patients with advanced SCNECP is generally higher, which may also affect immunotherapy efficacy. One study showed that patients with an ECOG score of 0 or 1 had better survival [28]. Therefore, there are only a few effective methods currently available in clinical practice. Development of novel antitumor agents is required to improve the prognosis of SCNECP. Antibody-drug conjugates have shown remarkable results in the treatment of breast cancer, and several clinical studies have been conducted on PC [29]. We expect that these drugs will improve the prognosis of SCNECP.

Conclusions

SCNECP is a rare and highly malignant tumor that is often transformed from CPAC treatment. It is difficult to be detected early, and most patients are diagnosed at an advanced stage. Therefore, the early detection of the transformation of CPAC into SCNECP is crucial. During CPAC treatment, if PSA continues to decrease while tumor markers such as CEA, CA199, and CA125 continue to increase, this may indicate that CPAC has begun to transform into SCNECP. The early detection of SCNECP transformation and timely radiotherapy may provide survival benefits to patients with limited-stage SCNECP. The survival time of patients with advanced SCNECP was short. Although the PFS after chemotherapy for advanced SCNECP is relatively short, chemotherapy is still the most effective treatment. Immunotherapy has shown encouraging results in other tumors; however, the results of SCNECP are unsatisfactory. We look forward to new drugs and treatment options to improve the prognosis of patients with SCNECP. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536351).

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Statement of Ethics

Ethical approval was not required for this study in accordance with the local guidelines. Written informed consent was obtained from the patient's daughter for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Funding was not required; hence, the funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Author Contributions

Binbin Song and Hong Pan are responsible for the research design, data interpretation, data acquisition, selection, and analysis, as well as the clinical interpretation of the data. Yan Luo and Li Qing contributed to the drafting of the report. Hong Pan and Dong Li have read, revised, and approved the final draft. All the authors have read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Bell PD, Huber AR, Agostini-Vulaj D. Clinicopathologic features of metastatic small cell carcinoma of the prostate to the liver: a series of four cases. Diagn Pathol. 2021;16(1):35.
2 Kelly K, Balk SP. Reprogramming to resist. Science. 2017;355(6320):29–30.
3 Ku SY, Rosario S, Wang Y, Mu P, Seshadri M, Goodrich ZW, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science. 2017;355(6320):78–83.
4 Labrecque MP, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, et al. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. J Clin Invest. 2019;129(10):4492–505.
5 Van Bos E, Dekuyper P, Gabriel C, Waterloos M, Van Baelen A, Huybrechts S, et al. Small cell carcinoma of the prostate after low-dose-rate brachytherapy: a case report. J Med Case Rep. 2020;14(1):203.
6 Zhang M, Shi W, Zhang QW, Wang W, Li QY. Diagnosis and treatment of small cell neuroendocrine carcinoma of the prostate. Zhonghua Nan Ke Xue. 2021;27(3):219–25.
7 Rao SR, Protheroe A, Cerundolo L, Maldonado-Perez D, Browning L, Lamb AD, et al. Genomic evolution and transcriptional changes in the evolution of prostate cancer into neuroendocrine and ductal carcinoma types. Int J Mol Sci. 2023;24:12722.
8 Akamatsu S, Wyatt AW, Lin D, Lysakowski S, Zhang F, Kim S, et al. The placental gene PEG10 promotes progression of neuroendocrine prostate cancer. Cell Rep. 2015;12(6):922–36.
9 Cantley RL, Wang X, Reichert ZR, Chinnaiyan AM, Mannan R, Cao X, et al. Metastatic prostate cancer diagnosed by fine-needle aspiration: contemporary cytopathologic and biomarker assessment with clinical correlates. Cancer Cytopathol. 2023;131(2):117–35.
10 Ida A, Okubo Y, Kasajima R, Washimi K, Sato S, Yoshioka E, et al. Clinicopathological and genetic analyses of small cell neuroendocrine carcinoma of the prostate: histological features for accurate diagnosis and toward future novel therapies. Pathol Res Pract. 2022;229:153731.
11 Lin X, Shi Q, Yang XJ. Cytomorphology, immunoprofile, and clinicopathologic correlation of metastatic prostatic carcinoma. Hum Pathol. 2022;130:36–46.
12 Alves D, Calmeiro ME, Silva R, Coelho H. Small-cell neuroendocrine cancer of the prostate: an atypical presentation of a common disease. BMJ Case Rep. 2016;2016:bcr2016216199.

13 Kaur H, Samarska I, Lu J, Faisal F, Maughan BL, Murali S, et al. Neuroendocrine differentiation in usual-type prostatic adenocarcinoma: molecular characterization and clinical significance. Prostate. 2020;80(12):1012–23.
14 Fine SW. Neuroendocrine tumors of the prostate. Mod Pathol. 2018;31(S1):S122–132.
15 Singh A, Cheedella NKS, Shakil SA, Gulmi F, Kim DS, Wang JC. Liver metastases in prostate carcinoma represent a relatively aggressive subtype refractory to hormonal therapy and short-duration response to docetaxel monotherapy. World J Oncol. 2015;6(1):265–9.
16 Albertsen PC. PSA testing, cancer treatment, and prostate cancer mortality reduction: what is the mechanism? Urol Oncol. 2023;41(2):78–81.
17 Caño-Velasco J, Herranz-Amo F, Peligros-Gómez I, Barbas-Bernardos G, Sola-Vendrell E, Hernández-Fernández C. Mucin-producing urothelial type prostatic adenocarcinoma with signet ring cells and increased Ca 19.9 and Cea. Case report and literature review. Arch Esp Urol. 2019;72(7):647–52.
18 Bray AW, Duan R, Malalur P, Drusbosky LM, Gourdin TS, Hill EG, et al. Elevated serum CEA is associated with liver metastasis and distinctive circulating tumor DNA alterations in patients with castration-resistant prostate cancer. Prostate. 2022;82(13):1264–72.
19 Jiang C, Zhao M, Hou S, Hu X, Huang J, Wang H, et al. The indicative value of serum tumor markers for metastasis and stage of non-small cell lung cancer. Cancers. 2022;14(20):5064.
20 Feuer JA, Lush RM, Venzon D, Duray P, Tompkins A, Sartor O, et al. Elevated carcinoembryonic antigen in patients with androgen-independent prostate cancer. J Investig Med. 1998;46(2):66–72.
21 Mollica V, Brocchi S, Dall'Olio FG, Marcolin L, Paccapelo A, Santoni M, et al. Tumor growth rate decline despite progressive disease may predict improved nivolumab treatment outcome in mRCC: when RECIST is not enough. Cancers. 2021;13(14):3492.
22 Wang J, Xu W, Mierxiati A, Huang Y, Wei Y, Lin G, et al. Low-serum prostate-specific antigen level predicts poor outcomes in patients with primary neuroendocrine prostate cancer. Prostate. 2019;79(13):1563–71.
23 Zaffuto E, Pompe R, Zanaty M, Bondarenko HD, Leyh-Bannurah SR, Moschini M, et al. Contemporary incidence and cancer control outcomes of primary neuroendocrine prostate cancer: a SEER database analysis. Clin Genitourin Cancer. 2017;15(5):e793–800.
24 Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–9.
25 Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):51–65.
26 Wee CE, Costello BA, Orme JJ, Quevedo JF, Pagliaro LC. Chemotherapy with atezolizumab for small cell or neuroendocrine carcinoma of the prostate: a single institution experience. Prostate. 2021;81(13):938–43.
27 Rizzo A, Santoni M, Mollica V, Fiorentino M, Brandi G, Massari F. Microbiota and prostate cancer. Semin Cancer Biol. 2022;86(Pt 3):1058–65.
28 Mollica V, Rizzo A, Marchetti A, Tateo V, Tassinari E, Rosellini M, et al. The impact of ECOG performance status on efficacy of immunotherapy and immune-based combinations in cancer patients: the MOUSEION-06 study. Clin Exp Med. 2023;23(8):5039–49.
29 Rosellini M, Santoni M, Mollica V, Rizzo A, Cimadamore A, Scarpelli M, et al. Treating prostate cancer by antibody-drug conjugates. Int J Mol Sci. 2021;22:1551.