Letter

Radical cystoprostatectomy with orthotopic neobladder for a case of treatment emergent neuroendocrine prostate cancer presenting as bladder mass with hematuria—a rare instance of tumor remission after local control

Dear editor

Treatment emergent neuroendocrine prostate cancer (t-NEPC) is most commonly observed after development of resistance to androgen deprivation therapy (ADT) and is associated with rapid progression and widespread metastases with survival less than 1 year from diagnosis [1]. Management of this disease is mainly through cytotoxic chemotherapy and there is no published evidence of treating the primary prostatic lesion in this stage of the disease, unlike that of localized prostate cancer or castrate sensitive metastatic prostate cancer [2]. In this letter, we report the only known case of t-NEPC who presented with an initial diagnosis of bladder urothelial carcinoma and was treated by early radical surgery and chemotherapy, which led to long-term disease control and preservation of quality of life.

A 60-year-old gentleman, a known case of metastatic adenocarcinoma prostate for the last 3 years, presented to us with complaints of gross, total painless hematuria with passage of clots of 3 months duration. His serum prostate-specific antigen (PSA) at initial presentation was 45.5 ng/dL and he had subsequently undergone ADT in the form of bilateral orchiectomy along with six cycles of docetaxel chemotherapy. One month after completion of docetaxel therapy, patient had achieved nadir PSA of 3.2 ng/dL, which gradually rose to 5.4 ng/dL, 7.1 ng/dL, 9.0 ng/dL, and finally to 11.4 ng/dL over the next 6 months. Tablet Abiraterone was then started for this patient at a dose of 1000 mg daily and the PSA again decreased to a nadir value of 1.2 ng/dL in the next 2 months. Patient was on regular follow-up at the center with monitoring of PSA levels for the next 12 months when he developed gross, total, painless hematuria and presented to us. Contrast enhanced computed tomography (CECT) scan of the abdomen revealed a strongly enhancing polypoidal mass lesion, measuring 6 cm × 6 cm, in the left posterolateral wall of the bladder extending inferiorly to involve the prostate. There was bilateral pelvic lymphadenopathy, with the largest lymph node being 1.9 cm × 1.8 cm in the left internal iliac region (Fig. 1A–1C). Magnetic resonance imaging (MRI) showed a polypoidal bladder mass which was contiguous with the prostatic mass. Bilateral seminal vesicles and neurovascular bundles were involved (Fig. 1D and 1E). Prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET CT) was done which showed no evidence of any distant metastases along with PSMA avid prostatic mass with intravesical component and pelvic lymphadenopathy (Fig. 2). Cystoscopy showed a large polypoidal growth about 10 cm × 7 cm arising from the left lateral wall, with multiple dilated blood vessels over the surface. Base of the growth showed multiple enlarged convoluted plexus of vessels. The growth was highly vascular with ooze from the entire surface and was bleeding on touch. Biopsy was taken from the growth which showed high grade lamina invasive transitional cell carcinoma (TCC) on histopathological examination (Fig. 3).

Post-operative period was complicated by hematuria with clot retention needing multiple cystoscopic evacuations and serial fall in hemoglobin, so the decision to go ahead with cystoprostatectomy was taken. On exploration, there was a hard growth palpable in the bladder. There were multiple conglomerate lymph nodes presenting bilaterally, with the largest being 5 cm × 5 cm present along the left internal iliac artery which was removed in toto ligation and division at the origin. Intra-operative frozen section of the bladder neck and the distal ureteric margins were done and confirmed to be free of tumor before proceeding with urinary diversion in the form of W-shaped orthotopic
neobladder. The final histopathology report showed neuroendocrine prostate cancer with foci of adenocarcinoma with metastases to bilateral pelvic lymph nodes (Fig. 4A–4C). Bilateral seminal vesicles as well as the lateral surgical margins of the prostate were involved by the tumor. Immunohistochemistry showed positive staining for chromogranin, synaptophysin, and PSA, confirming the diagnosis of neuroendocrine tumor of prostate (Fig. 4D and 4E). As per the histopathology report, patient was planned for adjuvant chemotherapy and local radiotherapy. He received six cycles of etoposide and carboplatin and 72 Gy external beam radiotherapy to the prostatic bed.

At 6 months follow-up, patient had PSA of 0.02 ng/dL. He was completely continent and did not have any evidence of disease on PET scan. At 2 years post-operation, patient continues to have a PSA level of 0.01 ng/dL without any evidence of disease recurrence on functional and cross-sectional imaging.

The increased use of second-line androgen receptor (AR) targeted therapies in treatment of prostate cancer in castrate naive setting [3,4] has led to the development of a distinct clinical and histologic subtype of castrate resistant prostate cancer called t-NEPC. Developing as a...
aggressive phenotype and has a uniformly poor prognosis. In pect neuroendocrine differentiation. t-NEPC is a very not check the same as we did not have any reason to sus-
have been shown to be elevated in cases of t-NEPC. We did
diagnosis. Serum carcino embryonic antigen (CEA) levels
adénopathy, which was persistent from the time of initial
tissue or bony metastases apart from the pelvic lymph-
aging and cross-sectional imaging did not reveal any soft
masses and a low PSA level relative to the tumor burden or
lineage plasticity, these tumors are
completely resistant to standard ADT and are highly meta-
able to assume that t-NEPC represents a large proportion of patients of CRPC who are progressing on second-line AR targeted treatment. Biopsies from metastatic sites in such patients have demonstrated t-NEPC in 10%–20% [7–9]. Usually the patients present with exclusively visceral or predominantly lytic bony metastases with bulky tumor masses and a low PSA level relative to the tumor burden or a short duration of response to AR targeted therapy [10,11].

Figure 4 HE and immunohistochemistry stained sections of the tumour from the resected surgical specimen. Top row: Mildly pleomorphic to isomorphic tumour cells arranged in nested configuration (200× magnification) (A); Tumour cells showing moderate nuclear atypia (400× magnification) (B); Periprostatic skeletal muscle infiltration by the tumour (200× magnification) (C). Bottom row (200× magnification): Microphotographs showing positive immunostaining for syn-
antophysin (D), chromogranin (E), and prostate-specific anti-
gen (F). HE, hematoxylin and eosin.

of lineage plasticity, these tumors are consequence of lineage plasticity, these tumors are completely resistant to standard ADT and are highly meta-
able and invasive [5,6]. Since therapeutic resistance is an universal phenomenon in prostate cancer, it would not be unwise to assume that t-NEPC represents a large proportion of patients of prostate cancer is being investigated in the ongoing TROMBONE trial and the recently published HORRAD trial [15,16]. The favorable results seen in our case may need to be validated in larger studies examining the effect of treatment of the primary site in patients of castrate resistant prostate cancer with bulky local disease and small distant metastatic burden. We would like to conclude by saying that rarely t-NEPC may present with symptoms of hematuria and bladder outlet obstruction without stigmata of metastatic bony or visceral disease. Poorly differentiated tumors may be mistaken for TCC. In such patients, radical local treatment with aggressive post-operative platinum-based chemotherapy may help in extending survival. a literature review of 123 t-NEPC patients, the time to development of t-NEPC from initial diagnosis of PC was 20 months, and the median survival after t-NEPC was just 7 months [2]. Although the first-line cytotoxic chemotherapy in the treatment of prostate carcinoma is docetaxel, the treatment of t-NEPC involves a platinum-based regimen similar to that used for small cell carcinoma of the lung. Based on multiple phase II trials, National Comprehensive Cancer Network (NCCN) recommends using a combination of either cisplatin or carboplatin with etoposide or enrol-
ment in a clinical trial for the treatment of such tumors [2,10,12,13]. Most patients enrolled in these trials had disease burdens and clinical features typical of t-NEPC. Our patient did not have any distant metastases and no soft tissue metastases apart from pelvic lymphadenopathy, so the option of biopsy from the primary site to detect variant histology was not available to us. Also the presence of an aggressively bleeding bladder mass, showing features of TCC on histopathology, made us consider this to be a more likely cause of cancer related morbidity and mortality to the patient than his prostate cancer which was apparently under control. Therefore, we planned to do a palliative cystoprostatectomy with urinary diversion. In our experi-
ence even patients with limited life expectancy have a good quality of life with orthotopic neobladder urinary diversion. Furthermore, our patient was in good general condition and had Eastern Cooperative Oncology Group (ECOG) 1 performance status [14]. Therefore, we made a W-shaped pouch with serous lined extramural uretero-ileal anastomosis for urinary diversion. In a study by Aparicio et al. [10], 113 patients were initially administered carbo-
platin and docetaxel for four cycles and more than 90% of the patients went on to receive second-line chemotherapy and showed disease progression even after that. Since our patient had already completed docetaxel based therapy and had progressed after that, it was decided that a course of carboplatin and etoposide should be administered. At the time of submitting this report, our patient continues to be on follow-up of 24 months and is free from serological or metastatic disease progression.

While the treatment done by us is not the standard of care for this type of prostate cancer, it provided the patient relief from symptoms and the subsequent local disease control and cytoreduction probably helped in the response to carboplatin based therapy. Though treatment of the pri-
mary lesion has not been described in the castrate resistant setting, local therapy in the setting of metastatic prostate cancer is being investigated in the ongoing TROMBONE trial and the recently published HORRAD trial [15,16]. The favorable results seen in our case may need to be validated in larger studies examining the effect of treatment of the primary site in patients of castrate resistant prostate cancer with bulky local disease and small distant metastatic burden. We would like to conclude by saying that rarely t-NEPC may present with symptoms of hematuria and bladder outlet obstruction without stigmata of metastatic bony or visceral disease. Poorly differentiated tumors may be mistaken for TCC. In such patients, radical local treatment with aggressive post-operative platinum-based chemotherapy may help in extending survival.
Author contributions

Study design: Rahul Jena, Nandita Chaudhary, Uday Pratap Singh.
Data acquisition: Rahul Jena, Uday Pratap Singh, Nandita Chaudhary, Hira Lal.
Data analysis: Rahul Jena, Hira Lal.
Drafting of manuscript: Rahul Jena, Uday Pratap Singh.
Critical revision of the manuscript: Uday Pratap Singh, Hira Lal.

Conflicts of interest

The authors declare no conflict of interest.

References

[1] Wang HT, Yao YH, Li BG, Tang Y, Chang JW, Zhang J. Neuroendocrine prostate cancer (NEPC) progressing from conventional prostatic adenocarcinoma: Factors associated with time to development of NEPC and survival from NEPC diagnosis—a systematic review and pooled analysis. J Clin Oncol 2014;32:3383–90.

[2] Flechon A, Pouessel D, Ferlay C, Perol D, Beuzeboc P, Gravis G, et al. Phase II study of carboplatin and etoposide in patients with anaplastic progressive metastatic castration-resistant prostate cancer (mCRPC) with or without neuroendocrine differentiation: Results of the French Genito-Urinary Tumor Group (GETUG) P01 trial. Ann Oncol 2011;22:2476–81.

[3] Ryan CJ, Smith MR, De Bono JS, Molina A, Logothetis CJ, De Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.

[4] Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;370:424–33.

[5] Bishop JL, Davies A, Ketola K, Zoubeidi A. Regulation of tumor cell plasticity by the androgen receptor in prostate cancer. Endocr Relat Canc 2015;22:R165–82. https://doi.org/10.1530/ERC-15-0137.

[6] Nouri M, Caradec J, Lubik AA, Li N, Hollier BG, Takhar M, et al. Therapy-induced developmental reprogramming of prostate cancer cells and acquired therapy resistance. Oncotarget 2017;8:18949. https://doi.org/10.18632/oncotarget.14850.

[7] Small EJ, Aggarwal RR, Huang J, Sokolov A, Zhang L, Alumkal JJ, et al. Clinical and genomic characterization of metastatic small-cell/neuroendocrine prostate cancer (SCNC) and intermediate atypical prostate cancer (IAC): Results from the SU2C/PCF/AACR West Prostate Cancer Dream Team (WCDT). J Clin Oncol 2016;34:5019. https://doi.org/10.1200/JCO.2016.34.15_suppl.5019.

[8] Nadal R, Schweitzer M, Kryvenko ON, Epstein JI, Eisenberger MA. Small cell carcinoma of the prostate. Nat Rev Urol 2014;11:213. https://doi.org/10.1038/nrurol.2014.21.

[9] Aggarwal R, Huang J, Alumkal JJ, Zhang L, Feng FY, Thomas GV, 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. https://doi.org/10.1200/JCO.2017.77.6880.

[10] Aparicio AM, Harzstark AL, Corn PG, Wen S, Araujo JC, Tu SM, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin Cancer Res 2013;19:3621–30.

[11] Turina CB, Coleman DJ, Thomas GV, Fung AW, Alumkal JJ. Molecular testing identifies determinants of exceptional response and guides precision therapy in a patient with lethal, treatment-emergent neuroendocrine prostate cancer. Cureus 2019;11. https://doi.org/10.7759/cureus.5197.

[12] Culine S, ElDemery M, Lamy PJ, Ibora F, Avances C, Pinguet F. Docetaxel and cisplatin in patients with metastatic androgen independent prostate cancer and circulating neuroendocrine markers. J Urol 2007;178:844–8.

[13] Papandreou CN, Daliani DD, Thall PF, Tu SM, Wang X, Reyes A, 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.

[14] Singh UP, Jena R, Madhavan Kumar, Kumar N, Sureka SK, Srivastava A, Radical cystectomy and W-shaped ileal orthotopic neobladder reconstruction with serosa-lined tunnelled ureteroileal anastomoses: A critical analysis of the short-term voiding patterns and urodynamic and functional outcomes. Indian J Urol 2019;35:121. https://doi.org/10.4103/iju.IJU_356_18.

[15] Boevé LM, Huushof MC, Vis AN, Zwinderman AH, Twisk JW, Witjes WP, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: Data from the HORRAD trial. Eur Urol 2019;75:410–8.

[16] Sooriakumaran P. Testing radical prostatectomy in men with prostate cancer and oligometastases to the bone: A randomized controlled feasibility trial. BJU Int 2017;120:E8–20. https://doi.org/10.1111/bju.13925.

Rahul Jena*
Uday Pratap Singh
Department of Urology and Renal Transplant, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Hira Lal
Department of Radiodiagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Nandita Chaudhary
Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

*Corresponding author.
E-mail address: jena.rahul@gmail.com (R. Jena)