Small cell carcinoma of the prostate after high-dose-rate brachytherapy for low-risk prostatic adenocarcinoma

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Received June 25, 2012; Accepted September 19, 2012

DOI: 10.3892/ol.2012.998

Abstract. In the present study, we describe an 80-year-old patient who developed prostatic small cell carcinoma (SCC) following high-dose-rate brachytherapy (HDR-BT) for low-risk prostatic adenocarcinoma. The patient received one implant of Ir-192 and 7 fractions of 6.5 Gy within 3.5 days, for a total prescribed dose of 45.5 Gy. A total of 27 months after HDR-BT, the patient complained of difficulty in urinating. His serum prostate-specific antigen (PSA) levels were 3.2 ng/ml. Systemic examination revealed an enlargement of the prostate, urethral stenosis, pelvic lymph node swelling and multiple lung and bone lesions. His serum neuron-specific enolase (NSE) levels were elevated to 120 ng/ml. A prostate needle biopsy was performed for pathological examination. Histologically, there were tumor cells with hyperchromatic nuclei and scant cytoplasm showing a solid or trabecular growth pattern. Immunohistochemically, they were positive for AE1/AE3, CD56 and synaptophysin, and negative for PSA, PAP and CD57. These findings are consistent with SCC of the prostate. A review of the prostate needle biopsy specimen prior to HDR-BT did not reveal any tumor cells positive for chromogranin A, nor synaptophysin. The final diagnosis was SCC of the prostate with local progression, with lung, lymph node and bone metastases. Three cycles of etoposide/cisplatin (EP) were administered. A greater than 50% decrease in the serum NSE levels was observed. However, there was no objective response. Due to the deterioration of the patient's general condition, EP was discontinued. One month later, his serum NSE showed a rapid increase to 210 ng/ml with aggressive local progression and the patient succumbed to the disease 5.5 months after the start of EP therapy.

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Key words: radiation therapy, chemotherapy, high-dose-rate brachytherapy, neuroendocrine differentiation, prostate cancer, small cell carcinoma, neuron-specific enolase

Introduction

Neuroendocrine differentiation is a basic feature of prostatic acinar cells. The identification of prostatic tumors with a neuroendocrine component has been reported to range from 10 to 100% by immunohistochemical studies (1,2). Neuroendocrine differentiation is characterized by the focal neuroendocrine cells commonly observed in conventional prostatic adenocarcinoma, but may also occur as rarer entities, including small cell carcinoma (SCC), carcinoid-like tumors and Paneth-like cells (3,4). Approximately 1% of prostate cancer in biopsies is reported to be SCC or neuroendocrine carcinoma, which is an aggressive form of cancer (5,6). The clinical features of SCC of the prostate include a markedly enlarged prostate, a disproportionately low prostate-specific antigen (PSA) level in the presence of metastatic disease, unresponsiveness to hormone therapy, visceral metastases and a high proportion of lytic to blastic bone lesions (7-9). This type of cancer may be identified at initial diagnosis or during androgen deprivation therapy, with or without conventional adenocarcinoma, and it is reported that SCC of the prostate was found in 10-20% of autopsy cases with a hormone-refractory state (10,11).

However, studies have indicated that radiation therapy affects the neuroendocrine differentiation of prostate cancer (12-14). Deng *et al* reported that the serum chromogranin A (CgA) level was elevated in 4 out of 9 patients following radiotherapy (14). However, no previous study has reported SCC of the prostate in a patient who underwent any type of radiation therapy to the prostate. This is the first study to report SCC of the prostate which arose following high-dose-rate brachytherapy (HDR-BT) for low-risk prostate cancer. The study was approved by the ethics committee of the University of Toyama, Toyama-shi, Japan. Written informed consent for the patient's family.

Case report

The patient was an 80-year-old Japanese male with no significant past medical history, with the exception of gastric ulcers at the age of 58 years. The patient was referred to the Department of Urology at Toyama University Hospital with elevated serum PSA of 6.45 ng/ml in October 2007. No abnormal findings were noted by a digital rectal examina-

Table I. Changes in the serum PSA levels prior to clinical progression.

		Time following HDR-BT (months)							
	Prior to HDR-BT	1	2	3	6	9	12	24	27
PSA (ng/ml)	6.50	6.75	3.49	3.03	2.71	2.82	3.05	3.20	3.23

PSA, prostate-specific antigen; HDR-BT, high-dose-rate brachytherapy.

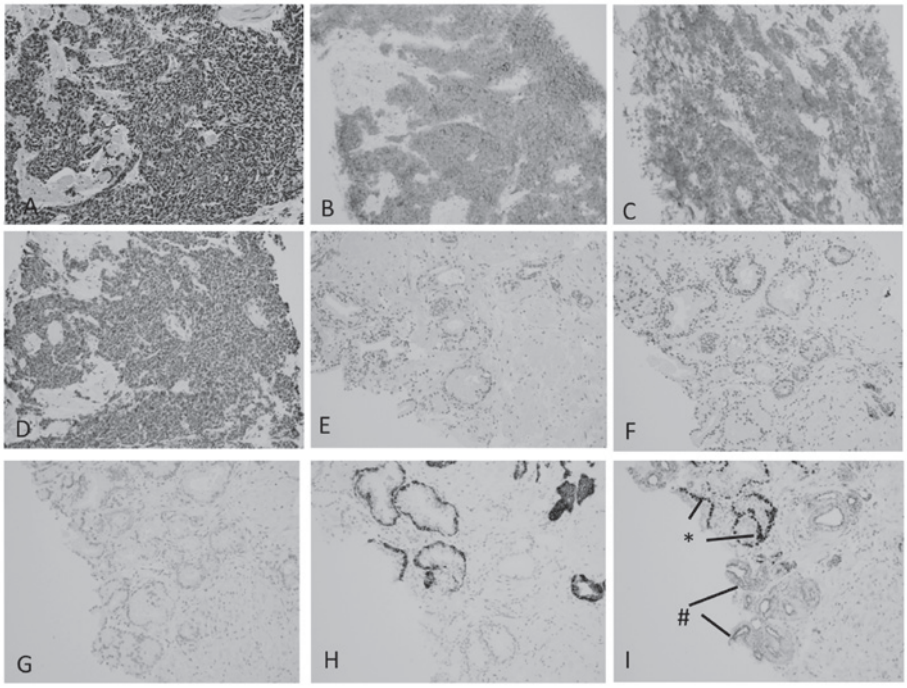


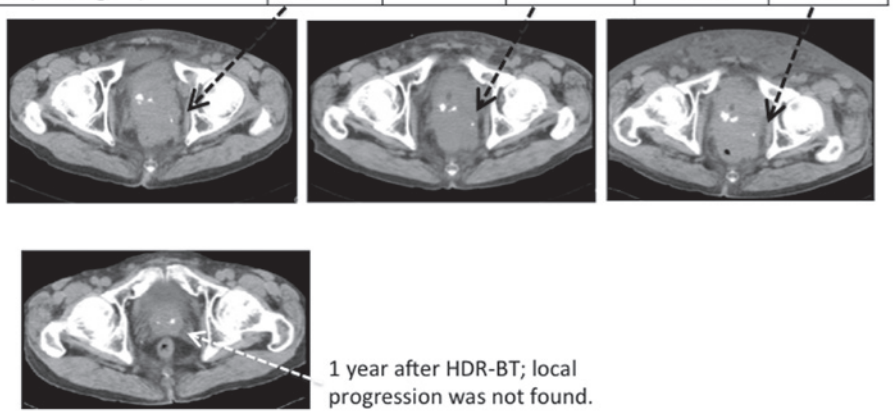
Figure 1. Pathological findings of the prostate needle biopsy. (A-D) Findings at the time of clinical progression (x20). (A) Hematoxylin and eosin staining. Tumor cells with hyperchromatic nuclei and scant cytoplasm showed a solid or trabecular growth pattern. (B) The tumor cells were positive for CD56. (C) The tumor cells were positive for synaptophysin. (D) The tumor cells were focally positive for chromogranin A. (E-I) Fndings at the initial biopsy (x20). (E) Hematoxylin and eosin staining demonstrated that the Gleason score was 3+3 adenocarcinoma. (F) The tumor cells were negative for chromogranin A. (G) The tumor cells were negative for CD56. (H) CK34bE12 staining was positive in benign glands. (I) *p63 and #P504S staining. p63 was positive in benign glands and P504S was positive in atypical glands without p63 expression.

tion. A transrectal 10-core prostate needle biopsy revealed low grade adenocarcinoma of the prostate in three cores. The patient's Gleason score was 3+3=6. Computed tomography, MRI, transrectal ultrasonography and a bone scan revealed the clinical stage to be organ confined, T2aN0M0, low-risk prostate cancer (15). In January 2008, the patient received one implant of Ir-192 and 7 fractions of 6.5 Gy within 3.5 days, for a total prescribed dose of 45.5 Gy, and was treated without any significant adverse events. The PSA nadir was 2.7 ng/ml at 6 months after HDR-BT.

During the follow-up at another hospital, the patient complained of hip discomfort, numbness and difficulty urinating 27 months after HDR-BT without PSA progression (Table I). Digital rectal examination, urethroscopy, computed tomography and a bone scan revealed enlargement of the prostate without induration, urethral stenosis, swelling of multiple pelvic lymph nodes, multiple lung lesions and multiple suspected bone metastases. His serum level of neuron-specific enolase (NSE) was elevated to 120 ng/ml (normal level, <10 ng/ml). The patient underwent a prostate needle biopsy (4 cores) for a pathological examination in April 2010. Histologically, the tumor cells with hyperchromatic nuclei and scant cytoplasm showed a solid or trabecular growth pattern (Fig. 1A). Immunohistochemically, these tumor cells were positive for AE1/3 (not shown), CD56 (Fig. 1B) and synaptophysin (Fig. 1C), focally positive for CgA (Fig. 1D) and TTF-1 (not shown) and negative for PSA, PAP and CD57 (not shown). There was no component of conventional prostatic adenocarcinoma noted. A review of the prostate needle biopsy specimen obtained prior to HDR-BT did not reveal the carcinoma to be positive for CgA (Fig. 1F), CD56 (Fig. 1G) nor synaptophysin (not shown), whereas CK34bE12 (Fig. 1H) and p63 (Fig. 1I) were positive in benign glands and P504S was positive in atypical glands without p63 expression (Fig. 1I). One week after the second biopsy, the patient experienced acute urinary retention and a Foley catheter was inserted.

The final diagnosis was SCC of the prostate with local progression and lung, lymph node and bone metastases.

Markers (reference value)	Before EP	After EP#1	After EP#2	After EP#3	2 months after EP
NSE (<10 ng/ml)	**122**	23.4	**33.0**	43.1	**232**
ProGRP (<46.0 pg/ml)	**23.8**			22.6	**21.4**
PSA (<4.0 ng/ml)	**2.240**			1.390	**2.330**



1 year after HDR-BT; local progression was not found.

Figure 2. Changes in the serum markers and computed tomography scans. The serum NSE level showed a greater than 50% decrease following EP therapy. The serum PSA and ProGRP levels remained low. Computed tomography scans showed no objective response in the enlarged prostate. EP, etoposide/cisplatin; NSE, neuron-specific enolase; ProGRP, Pro-gastrin-releasing peptide; PSA, prostate-specific antigen; HDR-BT, high-dose-rate brachytherapy.

Three cycles of etoposide/cisplatin (EP) were administered. The treatments were 28 days apart. The doses of etoposide and cisplatin were 56 mg/m^2 and 80 mg/m^2, respectively. The doses were reduced from the original regimen (7) due to the patient's poor overall health status. His serum NSE level showed a greater than 50% decrease following EP therapy (Fig. 2), but no definitive objective response was observed. The adverse events (Common Terminology Criteria for Adverse Events v3.0, CTCAE) associated with EP therapy were grade 3 leukocytopenia, grade 2 anemia, grade 3 hypocalcemia, grade 4 hyponatremia, grade 1 creatinine elevation and grade 3 anorexia. There was also deterioration of his general condition, therefore, the patient discontinued EP therapy and started to receive best supportive care. One month later, the patient's serum NSE showed a rapid increase to 210 ng/ml with aggressive local progression and he succumbed to the disease 5.5 months after the initiation of EP therapy.

Discussion

SCC (neuroendocrine carcinoma) of the prostate accounts for 10% of all extra-pulmonary SCCs (16). It is estimated that approximately 1% of all prostate cancers are SCC (17). In approximately 50% of the cases, the tumors are mixed SCC and adenocarcinoma of the prostate. However, no study has reported this type of cancer arising following radiation therapy to the prostate in the literature. In the present patient, the HDR-BT itself may have caused the SCC in the prostate. It is also possible that the SCC existed at the initial diagnostic prostate biopsy, but was too small to be identified, or that the SCC developed by chance following the HDR-BT.

Previous studies have revealed that radiation therapy induces the neuroendocrine differentiation of prostate cancer. Changes in the levels of CgA and NSE were shown among hormone-refractory patients undergoing palliative radiation therapy for bone metastases by Hvamstad *et al* (12). The serum NSE value was decreased, whereas CgA and PSA were increased, after radiation. NSE and CgA have been used as serum neuroendocrine markers for neuroendocrine differentiation (18). Deng *et al* (13,14), reported that ionizing radiation (IR) induced neuroendocrine differentiation in prostate cancer cells through the interaction between CREB and ATF2. IR-induced neuroendocrine-like cells were resistant to docetaxel and androgen depletion-induced growth inhibition. The authors' pilot study in prostate cancer patients showed that the serum CgA level was elevated in 4 out of 9 patients following radiotherapy (14). Taken together, these findings provide evidence that radiation-induced neuroendocrine differentiation is a general therapeutic response in a subset of prostate cancer patients. However, radiation-induced SCC has never been reported in any specific organ.

However, certain studies have reported that co-existing adenocarcinoma and SCC share the same clonal origin. Hansel *et al* (19) reported that the same TP53 mutation was shared in morphologically and phenotypically distinct concurrent primary small cell neuroendocrine carcinoma and adenocarcinoma of the prostate (Gleason score 4+3=7). Williamson *et al* (20) demonstrated that ERG-TMPRSS2 rearrangement, the most frequent molecular alteration in prostate cancer, was shared by concurrent prostatic adenocarcinoma and prostatic SCC, and was absent in SCC of the urinary bladder as evidence supporting the monoclonal origin of the prostate cancers. Therefore, the SCC in this patient may have had the same origin as the Gleason 3+3 adenocarcinoma.

SCCs of the prostate are thought to be identical to SCCs of the lung. Therefore, cisplatin-based cytotoxic agents that are similar to those used for SCC of the lung are usually applied, such as irinotecan + cisplatin or etoposide + cisplatin (2,21,22). In the present patient, treatment with etoposide and cisplatin was effective in terms of the serum marker response; however, it was impossible to continue this therapy due to deterioration of the patient's general condition. Recently, Deorah *et al*

showed that the median survival in 191 subjects with SCC of the prostate was 11 months, which falls within the range 5-17.5 months reported previously (23). The 12-, 24-, 36-, 48- and 60-month observed survival rates were 47.9, 27.5, 19, 17 and 14.3%, respectively, in patients with primary SCC of the prostate (23). Age, concomitant low-grade prostatic adenocarcinoma and the stage of the disease were the strongest predictors of survival for patients with prostatic SCC. The survival of the present patient following EP therapy was 5.5 months, which was shorter than the results in the literature. This may be due to the patient's characteristics, such as his older age (80 years), metastatic disease and pure SCC.

In conclusion, we present a case of SCC of the prostate with local progression and metastases to lung, pelvic lymph nodes and bones. This disease arose 27 months following HDR-BT monotherapy without PSA progression. This report alerts physicians to the possibility of neuroendocrine progression after radiotherapy, and confirms the importance of objective diagnostic imaging and physical examination, in addition to PSA testing, in the management of prostate cancer, even in patients who have localized and low-risk disease. If disease progression is unusual, as the case presented in this study, a prostate biopsy should be considered for pathological exploration.

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