Mixed Primary Small Cell Carcinoma of Prostate and Primary Adenocarcinoma of Prostate: A Report of Two Cases and Review of the Literature on Small Cell Carcinoma of Prostate

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Abstract

Background: Small cell carcinoma of the prostate gland is a rare pathologic subtype of prostate cancer with ‘unique’ clinical features.

Aims: To report the investigation and management of two patients with small cell carcinoma of the prostate gland within our health trust
To review the literature on small cell carcinoma of prostate

Case Reports
Case 1: A 78-year-old man presented with a history of increasing lower urinary tract symptoms. His investigations which included a trans-rectal ultrasound scan of the prostate and a biopsy as well as an MRI-scan of the abdomen and pelvis confirmed that he had a mixture of primary small cell carcinoma of prostate and primary adenocarcinoma of prostate which was staged as T3b / 4, N1, M1b.
He was treated by means of LHRH analogue, and 3 cycles of chemotherapy (Carboplatin and etoposide). However, after 7 months there was evidence of progression of the disease as well as evidence of bony metastasis for which he had radiotherapy. He is being managed by a multidisciplinary team and being followed up at six weekly intervals.

Case 2: A 66-year-old man presented with discomfort from his haemorrhoids and difficulty evacuating his rectum. His investigations including clinical examination, trans-rectal ultrasound scan biopsies of prostate as well as MRI scan of abdomen and pelvis confirmed he had aT4 primary mixed small cell carcinoma and adenocarcinoma of prostate. He was treated by means of (a) hormonal treatment (casodex and zoladex initially and later on stilbesterol); (b) Combination chemotherapy (carboplatin and etoposide) as well as (c) radiotherapy.
He continued to have progressive disease and died after 3 years as a result of the small cell carcinoma.

Discussion: Small cell carcinoma is a rare variant of prostate cancer.
Small cell carcinoma is extremely aggressive and resistant to available therapies with a median survival range of 5 to 17 months.

Introduction

Neuroendocrine differentiation in carcinoma of the prostate assumes one of three forms which include:

- Small cell carcinoma
- Carcinoid like tumours
- Conventional adenocarcinoma of the prostate in association with focal neuroendocrine differentiation [1].

Small cell carcinoma of the prostate is a pathologic subtype of prostate cancer with unique clinical features which accounts for about 1% to 2% of malignancies of the prostate gland.
Small cell carcinoma of the prostate, unlike the typical adenocarcinoma of the prostate, does not have bone tropism; it also does not express prostate specific
antigen (PSA) at the same levels as those of adenocarcinoma of the prostate [2].

In addition to disparities in the distribution of metastases, there are disparities in the characteristics of the bony metastases emanating from small cell carcinoma in comparison with those emanating from adenocarcinoma [2].

Adenocarcinomas of the prostate are characterized by the development of dense blastic metastases, whereas small cell carcinomas of the prostate typically produce lytic bone metastases [2]. These unique features permit clinicians to suspect the diagnosis of small cell carcinoma of the prostate before the histological confirmation of its presence [2].

In view of the fact that cases of small cell carcinoma of the prostate are rarely encountered by clinicians, most clinicians may not be conversant with the biological behaviour of these aggressive tumours.

Two cases of mixed primary small cell carcinoma of the prostate and primary adenocarcinoma of prostate are reported in this paper together with a review of literature on small cell carcinoma of the prostate.

Case Reports

Case 1
A 78-year-old man was referred with a 2 to 3 month history of increasing difficulty in urinary-voiding; he presented with a history of poor urinary flow, and dribbling of the urine. The referring doctor had started him on Tamsulosin 400 micrograms orally daily and this had produced some benefit. However, his IPSS score at his initial consultation was 22/33 and his quality of life score was 3/6 indicating persistent moderate urinary tract symptoms. His co-morbidities were noted to be ischemic heart disease and hypertension.

His general examination on initial consultation was unremarkable; on abdominal examination there was evidence of a painless palpable bladder. On rectal examination his prostate gland was found to be very-enlarged with the right lobe feeling hard suggestive of stage T2 to T3 prostatic neoplastic disease. A provisional diagnosis of chronic retention of urine due to a stage T2/T3 prostatic carcinoma was made. He was therefore admitted to have investigations and monitoring of his urine output.

Some of his initial investigations and results were as follows:
- Full blood count – Haemoglobin 13.9 g/dL (normal range 13.0 – 18.0), White blood cell count (WBC) 7.9 x 10*9/L, (normal range 4.0 -11.0); Platelets 179 x 10*9/L
- Coagulation screen INR 1.1 (normal range 0.9-1.1); PT 13.0 s (normal range 10-15); Fibrinogen Derived 4.0 g/L (normal range 1.7 – 4.0)
- Serum Urea and Electrolytes – Serum Sodium 145 m-moles/L (normal range 136 – 145), Serum Potassium 3.2 m-moles/L, (normal range 3.5 – 5.4), Serum Creatinine 88 umol/L, (normal range 62-115), Serum Urea 4.6 m-moles/L (normal range 2.5 -6.7), Estimated GFR (eGFR “MDRD formula”) 70 mL/min (normal range > 60).
- Serum PSA – 17.9 ug/L (normal range
- Mid stream urine - flow cytometry studies White blood cells 3 /uL (normal range 0-10), Red blood cells 5 / uL (normal range 0-35 Epithelial cells normal); culture no growth.

He had a trans-rectal ultrasound scan of the prostate gland on the same day which revealed a prostate size of 60 cc (60 grams) with evidence of bilateral hypo echogenic areas; the prostatic capsule and seminal vesicles looked normal. Prostate biopsies were taken (10 specimens from each lobe). He was then catheterised per urethra draining 1,000 ml of clear urine.

The following findings were made on histological examination:
(a) Right lobe of prostate – total number of cores 13; total length of cores 113 mm; evidence of adenocarcinoma with modified Gleason score 7 (3+4) (see illustrations 1 and 2); cores containing tumour 1 of 13; total percentage of cancer 5%; additional microscopic features of peri-neural invasion; there was no evidence of associated high grade PIN; there was evidence of chronic inflammation; the adenocarcinoma was confirmed by the absence of basal stains with CK34BE12/p63 and granular cytoplasm with Racemase; there was also evidence of a small cell carcinoma present in 7 out of 13 cores (see illustrations 1, 2, 3 and 4) and this accounted for 10% which showed positive staining for neuroendocrine markers (CD56 and synaptophysin [see illustrations 5 and 6]) and TTF1 (see illustration 7); this small cell carcinoma tumour was negative for prostate markers (PSA and PAP) as well as negative for CDX2. Based upon these findings it was felt that the tumour should be best regarded as a combined adenocarcinoma and a small cell carcinoma but the possibility of a metastatic small cell carcinoma could not be entirely excluded. It was recommended that the case should be discussed at the next multi-disciplinary team meeting with a full clinicopathological and radiological correlation.

(b) Left lobe of prostate – total number of cores 11;
The case was discussed at the Specialist Multi-Disciplinary Team meeting and after reviewing the patient’s notes, the histology of the tumours as well as the CT-scan, MRI-scan and the bone scan the Multi-Disciplinary Team concluded that the histology revealed a mixture of adenocarcinoma of prostate and small cell carcinoma of prostate (this was a primary mixed tumour of the prostate); the staging of the tumour was T3b/4 N1. The Multi-Disciplinary Team recommended that the patient should be commenced on hormonal treatment for the adenocarcinoma and chemotherapy for small cell carcinoma of prostate.

He was reviewed by the urologist as well and was also seen by the Urology specialist nurse who explained the diagnosis and the recommended plans of management to him. He was treated by means of cyproterone acetate 100 mg orally three times a day for a month and his LHRH analogue injections were started after two weeks of commencement of the cyproterone acetate medication. He was also referred to an oncologist as recommended by the Specialist Multi-Disciplinary Team.

He initially had a successful trial without catheter but was readmitted 3 months later in retention of urine requiring catheterisation but failed subsequent trial without catheter and was re-catheterised and discharged home with a urethral catheter in-situ.

He was also seen by the oncologist two months later, by which time he had had monthly injections of LHRH agonists. The oncologist observed that the patient’s general condition had deteriorated significantly over the preceding 4 to 6 weeks despite being treated with LHRH agonist. He was counselled and consented for single agent Carboplatin in the first instance. It was also explained to him that he was at risk of bleeding which puts him at risk in view of the fact that he had an abdominal aortic aneurysm. It was explained to him that chemotherapy would provide him with the best chance of gaining control of his small cell carcinoma of prostate. His General Practitioner was advised to change his LHRH monthly injections to a 3 monthly preparation in order to limit the number of injections he would have in a year. He received his initial Carboplatin chemotherapy and was scheduled to have follow-ups at 3 weekly intervals. He tolerated the single agent Carboplatin very well following which he had an MRI Scan which showed slight disease progression within the vesico-prostatic mass and left sacral metastasis; other lymph glands showed stable disease. Following this he had 3 cycles of Carboplatin and Etoposide. During his chemotherapy treatment he was anaemic and required a total of 4 units of blood transfusion. He tolerated his further
chemotherapy well and MRI scan 6 months after his initial diagnosis showed some slight improvement in the lymph nodes and a small increase in size in the bone metastasis which was considered not significant. He then received 8 fractions of palliative radiotherapy 30Gy in 8 fractions to his pelvis which he completed by end of the 7th month after his initial diagnosis. His serum PSA at 7 months was 2.0 u-g /L. He remained in good spirit and was scheduled to attend Oncology follow-up after six weeks and Urology follow-up after another 3 months. He would continue to have regular Oncology and urology follow-ups as well as further CT scans, and blood tests in order to assess his progress.

Case 2
A 66-year-old man was referred to a general surgeon because of discomfort from his haemorrhoids. He had also been having some difficulty evacuating his rectum and in passing urine. In addition he had noticed that his long standing right inguinal hernia had become a bit uncomfortable / painful recently. He did not have any other significant past medical history and was not on any medication. His general and systematic examinations were reportedly normal except for the presence of a large right inguino-scrotal hernia. On inspection of his anal region large skin tags and prolapsing haemorrhoids were found and on digital rectal examination the general surgeon found a rock-hard rectal mass which extended anteriorly and this mass was adjudged to be extra-rectal but contiguous with the prostate gland and this finding in the opinion of the general surgeon was suspicious of a prostate cancer. In view of these findings the patient was referred for a urological opinion.

At the first urology consultation, clinical examination of the patient confirmed the presence of a right inguino-scrotal hernia, an expansile infra-renal aorta consistent with an abdominal- aortic aneurysm; external anal skin tags, haemorrhoids and in addition digital rectal examination findings were consistent with a large stage 4 prostate cancer. In view of the fact that the patient’s serum PSA done at the general surgical consultation was reported to be 7.0 ug /L, the urologist suspected that the patient may have an undifferentiated prostate cancer. The following investigations which were done were reported as follows:

Trans-rectal prostate biopsy – histological appearances of the biopsy specimens were consistent with very poorly differentiated tumour with differential diagnoses of prostate cancer, bladder cancer, and rectal cancer. The tumour on immunohistochemistry was negative for PSA but positive for PAP. The pathologists making the diagnosis were of the opinion that the tumour was a poorly differentiated prostatic carcinoma.

Isotope Bone Scan
CT scan – locally invasive prostate cancer (T4) and para-aortic nodal mass but there was no evidence of distant disease
Flexible cystoscopy – the urethra, urinary bladder and both ureteric orifices were normal; the prostatic urethra and the trigone were slightly distorted.

Based upon the provisional histology results the urologist commenced the patient on casodex and Zoladex and referred him to an oncologist to be considered for radical radiotherapy. Three months later his lower urinary tract symptoms had improved in that his previous nocturia had improved to voiding only once at night and his serum PSA was reported as 0.5 nanograms /ml.

At urology follow-up nine months after his initial referral his perineal discomfort had increased and clinically rectal examination revealed that the prostatic tumour appeared more locally advanced

Ten months after his initial referral he was admitted as an emergency with a 4 weeks history of increasing difficulty in passing urine. Clinical examination revealed he had retention of urine and on catheterisation he was found to have a residual urine volume of 1600 millilitres; his serum creatinine was then 992 u-mol/L (normal range 62-115 u-mol/L); and ultrasound scan showed right hydronephrosis. He was then transferred to the regional oncology centre.

At the Regional Oncology centre the histology of the prostate biopsy specimen was reviewed. The consensus opinion was that there was a mixture of poorly differentiated adenocarcinoma and small cell carcinoma of the prostate gland (see illustrations 10 and 11 which show the small cell carcinoma component of the tumour and 12 to 15 which illustrate the immunohistochemical staining of the small cell carcinoma). In view of the diagnosis he was given chemotherapy in the Regional Oncology centre where he received Carboplatin and Etoposide therapy following which he was adjudged to have stable disease 13 months after his initial referral. At follow-up 13 months after his initial referral he had some pelvic symptoms therefore the oncologists felt that it would be reasonable for him to be given palliative radiotherapy and also in view of the fact that he had an initial good response to hormonal therapy a second line hormonal treatment would be appropriate. He was therefore started on stilbeostrol 1 mg orally once a day accompanied by Aspirin 75 mg once a day.

Twenty six months pursuant to his initial referral he was admitted to the urology unit with voiding difficulties and raised serum creatinine of 340
(u-mol/L). His serum PSA during this admission was 3.5 ng / ml. He had an ultra-sound scan of renal tract which showed gross hydronephrosis of the right kidney and moderate left hydrenephrosis. He was also diagnosed with a right common femoral and popliteal deep vein thrombosis. A supra-pubic catheter was inserted under ultrasound scan guidance in theatre to relieve the bladder obstruction. He was commenced on warfarin and after his serum urea and electrolytes had gradually improved he was discharged home and also referred to the Regional Oncology centre for further assessment in order to be considered for additional treatment that may be advised by the Oncologists. An MRI scan was requested which confirmed extensive carcinoma of prostate infiltrating the right ureter, bladder, and rectum. He also complained of lower back pain and the MRI scan showed some metastases in the sacral area in view of this the oncologists were asked to consider for radiotherapy.

He received palliative radiotherapy but subsequently his general condition gradually deteriorated over a period of one year and he was managed by the Urology team, the oncology team as well as the palliative care team. His main problems were:

- Intermittent haematuria
- Gross lymphoedema and inability to mobilise due to discomfort and size of his genitals; Clinical examination revealed gross lymphoedema to the scrotal area, the penis, pelvis, and both distal and proximal region of the legs
- He had left nephrostomy inserted for obstructed left ureter which required regular changes of nephrostomy tubes at intervals and flushing of blocked nephrostomy tube.

The management of his lymphoedema included:
1. An extra large support made to measure fitting provided
2. Below knee hosiery in attempt to improve mobility
3. Simple lymphatic drainage techniques were demonstrated
4. Being referred to a podiatry team
5. Being placed on diuretics which were reviewed by the patient’s general practitioner
6. Regular follow-up and continuing support and advice provided by the lymph oedema Service team

**Discussion**

Small cell carcinoma of the prostate is a high-grade malignant neoplasm with neuro-endocrine differentiation. The typical morphologic features include:

- Small tumour cells with minimal cytoplasm
- Nuclear moulding,
- Fine chromatin pattern,
- Extensive tumour necrosis / apoptosis,
- A brisk mitotic rate [3].

Small cell carcinoma of the prostate accounts for less than 1% of all prostate cancers. About 50% of patients have pure small cell carcinomas at initial presentation. About 25% to 50% of cases are mixed with a conventional adenocarcinoma of prostate [4].

Another 25% to 40% of cases are initially diagnosed as adenoarcinoma of prostate and recur as small cell carcinoma after hormonal therapy. The median interval between initial diagnosis of adenocarcinoma of prostate and small cell carcinoma is 25 months [4, 5].

The mean age of diagnosis of small cell carcinoma of prostate is 65 to 69 years, which is similar to the average age of adenocarcinoma of prostate [5].

The risk factors pertaining to the development of small cell carcinoma of prostate include: age, race, and family history [6].

Men older than 60 years of age are typically affected by small cell carcinoma of prostate and the overall risk increases with age [5].

Some of the ethnic variations in the incidence of prostate cancer have been attributed to diet [7].

Red meat consumption and high-fat diet are considered possible risk factors. For example Asians have the lowest incidence of prostate cancer, and Asian immigrants to the USA who have adopted western style diets have an increased incidence but still less than the white population [5]. Other life style factors including sexual practices and occupation are at present not considered to be important factors relating to the development of prostate cancer [5].

Some prostate cancers may have a genetic component. There is a ten-fold increased risk for patients with two or more relatives. A patient who has a first-degree-relative with adenocarcinoma of the prostate has a two-fold increased relative risk [5]. The risk of prostate cancer decreases with distance in the ‘family tree,’ that is first versus second cousins [5].

With regard to location, the distribution of small cell
carcinoma of prostate is similar to that of adenocarcinoma of prostate. [5] Most patients have multi-focal disease but also have a dominant nodule, located on the peripheral zone. These tumours may be palpable by digital rectal examination and can be diagnosed by needle core biopsy; transition zone and central zone are not common for clinically important prostate cancer. [5]

The presenting symptoms, of patients with small cell carcinoma of prostate, are similar to those of patients who have adenocarcinoma of prostate. Localized tumours produce few if any symptoms. Patients who have symptoms usually have locally advanced or metastatic disease. [5] A number of patients notice a change in their urinary stream with trouble initiating and stopping. [5]

Patients with small cell carcinoma of prostate may have a number of symptoms including: urinary urgency, haematuria, haemospermia, or trouble with defecation. On digital rectal examination a nodule may be palpable. The development of bony metastasis is associated with bone pain and or fracture.

The serum prostate specific antigen (PSA) level is not raised in most patients with small cell carcinoma of the prostate unlike those patients with adenocarcinoma of the prostate. About 10% of patients with small cell carcinomas of prostate secrete hormones such as: adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH) and these patients may present with paraneoplastic syndromes. [8]

Tetu and associates [7] stated that small cell carcinomas of the prostate tend to invade outside the prostate and more commonly involve the surrounding organs, regional lymph nodes and distant organs than conventional adenocarcinomas and that the findings of metastatic spread or paraneoplastic syndrome should raise the suspicion of a small cell carcinoma.

Gross examination of prostate cancer tends to reveal a subtle yellowish-white colour with a firm feeling within the peripheral zone. Small cell carcinomas of the prostate have the same appearance as adenocarcinomas but they may feel some-what softer if significant necrosis is present. [5]

Nicholson and associates [9] stated that the microscopic features of small cell carcinomas of prostate are similar to those seen in small cell carcinomas in other organs.

Low-power microscopic view of small cell carcinoma of prostate reveals sheets of dark blue tumour cells with focal rosette formation and extensive necrosis. The chromatin of the tumour cells is delicate and may be damaged easily on the act of tissue processing leading to crush artefact. The basophilic DNA of tumour cells may also escape the nuclei and become entrapped in the blood vessel wall which is known as azzopardi effect.

Microscopic examination of small cell carcinoma of the prostate reveals the following features:

- The individual cells tend to be oval or angulated with scant cytoplasm;
- Indistinct borders and nuclear molding;
- The nuclei tend to be small (less than the diameter of 3 resting lymphocytes), although occasional larger cells may be present;
- The nuclear chromatin is finely granular (a salt-and-pepper pattern);
- The nucleoli are absent or small;
- Necrosis is a common feature as are frequent mitotic and apoptotic figures;
- The Gleason Grading System is not used for small cell carcinomas of prostate; as such tumours are poorly differentiated or high grade.

In patients whose prostatic tumours are co-existing adenocarcinoma and small cell carcinoma, the 2 components are intermixed in majority of cases whilst in about 20% of cases, there are distinct zones of small cell carcinomas and adenocarcinomas. [4] The adenocarcinoma is quite often high-grade (Gleason score > 7) and comprises a smaller portion in comparison with the small cell carcinoma. It is quite often very difficult to differentiate small cell carcinoma from high-grade adenocarcinoma, especially Gleason 5. In such difficult cases, the presence of rosettes, nuclear molding, and a fine chromatin pattern without prominent nucleolus help to identify small cell carcinoma. Immuno-histochemical staining of the tumours helps in the establishment of the diagnosis of small cell carcinoma of prostate. Morphology remains the criterion standard for the establishment of a diagnosis of small cell carcinoma. [10]

Pathologists who are suspicious of small cell carcinoma of the prostate do confirm the diagnosis by means of neuro-endocrine markers. The ensuing tumour markers are typically used (see illustration 16):

- Chromogranin A;
- Synaptophysin;
- Neuron-specific enolase;
- CD56.

Typically, one or more of the aforementioned markers are positive in small cell carcinomas. Nevertheless, in a small proportion of tumours (about 10%), all the neuro-endocrine markers are negative, which does preclude, the diagnosis of small cell carcinoma as long as the morphology is typical. A useful typical feature is
the clot-like perinuclear staining pattern for cytokeratin.

About half of the cases are also positive for TTF-1 with a nuclear staining pattern. [11]

The aforementioned stains have been useful in differentiating small cell carcinoma from Gleason 5 pattern adenocarcinoma of prostate. Furthermore, non neuroendocrine stains are also helpful in view of the fact that unlike adenocarcinoma of prostate, small cell carcinomas are often negative for androgen receptor (AR), prostate specific antigen (PSA), prostatic acid phosphatase (PAP), and P504s (AMACR). (See table – Illustration 15)

Neuroendocrine cells can be found focally in all prostate adenocarcinomas. [12]

Immunohistochemical studies against neuroendocrine markers, like chromogranin A, highlight a few isolated cell clusters of neuroendocrine cells among the more abundant adenocarcinoma cells with luminal secretory features. [13]

These scattered neuroendocrine cells that are present in adenocarcinoma of prostate, unlike tumour cells in small cell carcinoma are regarded as post mitotic and non proliferative. It has been suggested that both genetic factors and environmental factors likely contribute to the development of adenocarcinoma of prostate. Potential genetic factors which have been suggested include:

- Gene mutation or polymorphism in androgen;
- AR (androgen receptor)
- Steroid 5-alpha reductase type II (SRD5A2)
- An enzyme responsible for the conversion of testosterone to dihydrotestosterone (DHT). [14]

It has been suggested that the length of a polymorphic CAG repeat v region in the first exon of the AR gene appears to explain the racial differences in the incidence of prostate cancer. It has been found recently that in about half of the cases there is recurrent chromosomal rearrangement resulting in the fusion of transmembrane serine 2 (TIMPRESS 2) and a member of the ETS family transcription factors, most commonly ERG. [15].

It has been stated that the genetic changes specific to prostatic small cell carcinoma have not been studied in great detail. [16]

Tanaka and associates [17] stated that:

- The genetic features may be similar to adenocarcinoma of prostate but may contain additional genetic alterations which make such tumours androgen independent and more aggressive
- This may be particularly true in those tumours which are recurrent tumours in patients who were treated with hormonal therapy for a conventional adenocarcinoma.

Williamson and associates [18] have illustrated that 45% to 47% of small cell carcinomas of the prostate harbour ERG gene rearrangement, a number that is seen in adenocarcinoma of prostate.

Lotan and associates [19] showed that in cases of coexisting small cell carcinoma and adenocarcinoma, the majority exhibit concordant ERG gene rearrangement in the 2 components.

The aforementioned observations would suggest that small cell carcinoma of prostate may share a common origin with adenocarcinoma. On the other hand, it may arise from the latter ensuing additional genetic alterations. It is not clear how small cell carcinoma of prostate may be related to small cell carcinoma in other organs.

It has been suggested that all small cell carcinomas, irrespective of origin possess the identical morphology and immunohistochemical profile, thus possibly possessing similar genetic alterations. [20], [21], [22].

Simon and associates [23] showed that CD44, a putative cell surface marker for normal and cancerous stem cells in multiple organs, including the prostate gland, is expressed in small cell carcinomas of the prostate but is infrequently expressed in small cell carcinomas of other organs.

The histological differential diagnoses of small cell carcinoma of prostate include:

- Non Hodgkin’s lymphoma;
- Metastatic small cell carcinoma;
- High grade adenocarcinoma of prostate. [5]

Erasmus and associates [24] stated that with regard to spread and staging of small cell carcinomas of prostate:

- They may pursue similar routes as adenocarcinoma of prostate to spread to other parts of the body.
- They may invade through the prostatic capsule to involve the peri-prostatic soft tissue, seminal vesicles, bladder neck, and rectum locally.
- They may also metastasize to the pelvic lymph nodes, peri-aortic lymph nodes, bone, liver, adrenal glands, lung, and brain.
- The tumours are aggressive and tend to spread much earlier.
- The tumours present at a higher pathologic stage than adenocarcinoma of prostate.
- The tumour staging is the same as for adenocarcinoma of prostate.

Tetu and associates [7] stated that the prognosis of small cell carcinoma of prostate is less than 1 year.
There appears to be no significant survival difference between pure prostatic small cell carcinomas and mixed small cell / adenocarcinomas. Tumour stage is considered the single most important factor, even though any small amount of small cell carcinoma component is considered to carry a poor prognosis. [5]

In view of the rarity of small cell carcinomas of prostate, individual urologists or oncologists have limited experience in its management. Brown and associates [25] stated that small cell carcinomas of the prostate do not respond to hormonal therapy or radiotherapy, and surgery is usually not curative.

Amato and associates [26] stated that patients with small cell carcinoma of prostate are usually treated in the same manner as those patients with pulmonary small cell carcinomas with a regimen of cisplatin and etoposide.

It has been stated that most patients with small-cell carcinoma of the prostate are symptomatic at diagnosis, unlike patients with prostatic adenocarcinoma alone. [28] Palgren and associates stated that the signs and symptoms, in order of frequency, include obstructive, neurologic, and constitutional symptoms, followed by symptoms from paraneoplastic syndromes, bone pain, hydronephrosis, abdominal pain, hematochezia, and hematuria. [27]

Some authors have observed that the clinical features of small-cell carcinoma of the prostate include a markedly enlarged prostate, disproportionately low PSA levels in the presence of metastatic disease, unresponsiveness to hormone therapy, visceral metastases, and high proportion of lytic to blastic bone lesions. [26], [28], [29]

According to some authors, [1], [30], small-cell carcinoma of the prostate, accounts for 0.5% to 2% of all prostate malignancies.

It has been reported that the median survival time is poor for patients with small-cell carcinoma of the prostate, ranging from 5 months to 17.5 months. [7], [26], [28], [29], [30], [31].

The recommended treatment regimens for small-cell prostate cancer are similar to those for small-cell carcinoma of the lung and Chemotherapy is regarded as the mainstay of treatment, [7], [27], [28], [29], [31] with radiation used to supplement local control or for palliation of symptoms in metastatic disease. [7], [28], [29]. Cisplatin and etoposide are the most commonly recommended agents, and a recent phase II trial showed that the addition of doxorubicin to this regimen added to toxicity but not survival. [31] For localized disease, surgery is often included, and it has been suggested that surgery may be curative. [32]

In one relatively large retrospective-univariate-analysis of 60 patients primary surgery was the only independent prognostic factor found for prolonged survival. [33]

Rubenstein and associates observed that in contrast to prostatic adenocarcinoma, PSA is an unreliable tumour marker for small cell carcinoma of prostate and it is usually normal, even when there is metastatic disease. [6] A study by Rubenstein and associates suggested that carcinoembryonic antigen is a more reliable marker, because increase and decreases in antigen levels were found with disease progression and regression, respectively. Recently the tumour marker neuron-specific enolase has been proposed as a prognostic indicator; high levels suggest a poor prognosis.

Despite treatment with chemotherapy, the prognosis of small cell carcinoma of prostate is extremely poor, with a reported median survival by Patel and associates to be 7 months. [34] Because of the rarity of the condition, no standard therapeutic regime has been universally adopted. Reported cases have on the whole been managed by chemotherapeutic regimens similar to those recommended for small cell lung cancer. The results, nevertheless, have not been as favourable. Additionally, small cell carcinoma of prostate, in contradistinction to adenocarcinoma has been found to be unresponsive to hormone therapy.

A potential target for the treatment of small cell carcinoma is the relaxin receptor RXFP1. Relaxin is a small peptide hormone expressed in several cancers such as those of endocrine origin. Its receptor, RXFP1 (a G-protein-coupled receptor), is expressed in androgen receptors’ positive and negative cancers, as well as in prostate germ cells. In PC3 prostate cancer cell lines, which include small cell neuroendocrine carcinoma, treatment of RXFP1 showed significant reduction of tumour size, decrease in cell proliferation and metastatic disease, and increased apoptosis. [35]

It is well known and accepted that Small cell carcinoma of the prostate is a rare, aggressive, and treatment refractory form of prostate cancer. No good form of treatment is yet known for this disease, and median survival from initial diagnosis is less than 2 years. Nevertheless, new data from a mouse model of small cell carcinoma of prostate (SCCP) has suggested that combining two well understood and widely available chemotherapeutic agents may have a significant clinical effect on patients with small cell carcinoma of prostate (SCCP). Tung and associates [36] used a mouse model of small cell carcinoma of prostate (SCCP) to show that:
• Irinotecan (at 20 mg/kg/day on days 1–3 and 8–10) completely arrested growth of human small cell carcinoma (SCCP) implants (xenografts) in their mice, with a small reduction in human tumour volume and only minor weight loss (7 percent) of the mice.

• Irinotecan (at 12 mg/kg, also on days 1–3 and 8–10) + cisplatinum had similar effect, but with less weight loss among the mice.

Tung and associates [36] concluded cautiously that “Irinotecan could be useful for therapy of refractory prostatic small cell carcinoma, in particular in combination with cisplatin.

The normal prostate gland is constituted of base cell, exocrine cell and nerve endocrine cell (Neuroendocrine cell, NE cell). The NE cell can secrete various neuro-secretions, including chromogranin A, B (CgA, CgB), NSE, parathyroid hormone-related peptide, calcitonin and gastrin. The NE cell can be identified through the immuno-histo-chemistry method by positive stain of a marker, such as CgA, Syn and NSE [4], [37], [38]. There are currently clinical studies with experiments having already confirmed a prostate gland cancer sufferer would appear NED inside the focus after endocrine treatment. Additionally, it has been suggested that the NED was an important factor which causes toleration to the endocrine therapy. [39], [40], [41], [42], [43].

It has been suggested that the research of future work should include particular emphasis on the research of the NED mechanism; especially the selectivity blockade of some signalling molecule to prevent or convert the NED of prostate cancer cell; there should also be work to identify how the materials the NE cells secretes through paracrine secretion or autocrine and which incentives exist in the growth of the non-androgen depending cell; there should be a design or creation of new chemotherapy medicine which aims at secretion of NE cell to improve the sufferer’s living quality and survival rate of prostate cancer. [44] It has been suggested that: the multiple methods, such as hormone therapy in combination with chemotherapy or transfer factor immunotherapy, can be used to raise the patient’s survival rate; Bombesin / gastrin releasing peptide (BN/GRP) secreted by NE cell are the new therapeutic agents to be employed in the treatment of small cell carcinomas of the prostate [45], [46].

It is hoped that in the near future, the treatment which aims at NED mechanisms would bring a new hope for neuroendocrine carcinoma of prostate sufferers. It has been suggested that the cell-based -drug-efflux assay hopefully can help know the required chemotherapy to be given to patients accurately and for a much shorter time which significantly benefits cancer patients. [47] It has been suggested that whether or not a Cell-based Drug Efflux Assay can be used to select suitable drug for chemotherapy of small cell prostate carcinoma needs to be investigated through a future study. [45]

Small cell carcinoma of prostate was first described by Wenk and associates [48]. Small cell carcinoma of prostate can occur as an initial event at the time of first diagnosis and is then thought to originate from neuroendocrine cells present in the epithelium of prostatic ducts / acini and in the endothelium of prostatic urethra. It may also develop in prostate cancer during progression to castration resistance induced by androgen ablation. The most widely accepted opinion is that small cell carcinomas of prostate arise from totipotential stem cells of the prostate that have the ability to differentiate into either epithelial or neuro-endocrine type carcinomas. The latter type is characterized by the absence of expression of androgen receptors (AR) and prostate-specific antigen (PSA) and by positive expression of synaptophysin (SYN) neuro-endocrine marker [49], [50]. Prostatic small cell carcinoma is an aggressive disease, often described as universally fatal [51]. Small cell carcinoma of prostate is typically diagnosed at an advanced clinical stage with rapid progression and insensitivity to hormonal therapy; patients have a median survival of 5 to 17 months [7], [29]. Prostatic small cell carcinoma shows similarity to small cell lung carcinoma (SCLC) in morphologic features [29] and in the expression pattern of some genes [52]. In view of this, the commonly used treatment of prostatic small cell carcinoma, that is, platinum-based chemotherapy and irradiation, was adopted from SCLC therapeutic modalities. A number of anti-cancer agents have been used in combination with cisplatin, including etoposide, cyclophosphamide, doxorubicin, and vincristine; other combinations that have been used are carboplatin plus etoposide or taxanes [27], [31], [53], [54].

Cisplatin-based chemotherapy plus radiotherapy has despite initial positive responses, failed to be effective and a standard therapeutic regimens for small cell carcinoma of prostate has not yet been adopted since this disease is rare [48]. At the moment chemotherapy using cisplatin in combination with etoposide is the most common treatment for small cell carcinoma of prostate.
In contrast to prostatic adenocarcinoma, Serum PSA is an unreliable tumour marker for small cell prostate carcinoma and is usually normal, even when there is metastatic disease. One study suggested that carcinoembryonic antigen is a more reliable marker, because increases and decreases in antigen levels are found with disease progression and regression respectively. [6] More recently, the tumour marker neuron-specific enolase has been proposed as a prognostic indicator; high levels suggest a poor prognosis. [6]

Conclusions

Small cell carcinoma is extremely aggressive and resistant to available therapies with a median survival range of 5 to 17 months. Literature review indicates that there is no standard chemotherapeutic regimen for the treatment of small cell carcinoma of prostate.

At the moment chemotherapy using cisplatin in combination with etoposide in addition to radiotherapy is the most common treatment for small cell carcinoma of prostate. Because of the aggressive nature of small cell carcinoma which eventually tends to lead to the death of patients a multi-disciplinary team approach is required in the management of patients at various stages of the disease and this should include Urologists, oncologists, pathologists, radiologists, Urology specialist nurses, pain team and palliative care team who have various roles to play in the diagnosis, treatment, follow-up and continuing supportive care of the patients at all stages of the disease.

In view of the poor prognosis of the disease associated with the current available treatment modalities there is an urgent need for researchers, oncologists and urologists to search for new therapeutic regimens that would improve upon the prognosis of patients with small cell carcinoma of prostate.

Acknowledgement

Acknowledgement to Dr Kenneth Uzoka, Consultant Radiologist at North Manchester General Hospital United Kingdom for putting the arrows on the lymph nodes in the MRI-scan images

References


Illustrations

Illustration 1

Figure 1

Case 1 Haematoxylin and Eosin staining X 2.5 Magnification
Prostatic core biopsy containing Gleason 3+4 =7 adenocarcinoma and small cell
carcinoma
Illustration 2

Figure 2

Case 1- Haematoxylin and Eosin Staining X 20 magnification
Prostatic core biopsy showing Gleason 3+4 adenocarcinoma
Illustration 3

Figure 3

Haematoxylin & Eosin staining X 10 Magnification
Prostatic core biopsy showing a small cell neuroendocrine carcinoma; the tumour is composed of poorly differentiated small and large polygonal blue cells with scanty cytoplasm.
Illustration 4

Figure 4

Haematoxylin and Eosin staining X 20 Magnification
Prostatic small cell neuroendocrine carcinoma composed of poorly differentiated pleomorphic blue cells arranged in sheets and groups.
Illustration 5

Figure 5

Immuno-staining of CD56 X 20 magnification
Prostatic small cell carcinoma showing positive reactivity with CD56
Illustration 6

Figure 6

Immunostaining of Synaptophysin X 20 magnification
Small cell neuroendocrine carcinoma of prostate showing reactivity with Synaptophysin
Illustration 7

Figure 7

Case 1: “Immunohistochemistry X 20 Magnification”
Small cell carcinoma of prostate showing positive staining with TTF1
Illustration 8

Figure 8

MRI-scan of pelvis showing enlarged prostate with tumour and lymph node involvement of tumour (arrow pointing towards lymph node involved by tumour)
Illustration 9

Figure 9

MRI-scan of pelvis showing pelvic lymph node involvement of tumour (arrow pointing towards lymph node involved)
Illustration 10

Figure 10

Case 2
Haematoxylin and Eosin staining X 10 magnification
Prostatic small cell neuroendocrine carcinoma exhibiting sheets of pleomorphic blue poorly differentiated cells
Case 2
Haematoxylin and Eosin staining X 20 magnification
Prostatic small cell neuroendocrine carcinoma showing large pleomorphic and hyperchromatic cells interspersed with small cells and spindle-shaped cells
Illustration 12

Immuno-staining for PAP X 60 magnification
Small cell neuroendocrine carcinoma of prostate showing reactivity with prostatic acid phosphatase
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Figure 13

Immuno-staining of CD56 X 20 magnification
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Figure 14

Immuno-staining for synaptophysin X 20 magnification
Small cell neuroendocrine carcinoma is showing positive staining with synaptophysin
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Figure 15

Immuno-staining for chromogranin X 40 magnification. Small cell neuroendocrine carcinoma is showing positive reactivity with chromogranin.
Illustration 16

Figure 16

### Immunohistochemical Markers useful for the Differential Diagnosis of Prostatic Small Cell Carcinoma and Adenocarcinoma

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>PSA</th>
<th>PSAP</th>
<th>P504s</th>
<th>TTF-1</th>
<th>CD56</th>
<th>Chrom A</th>
<th>Synapt</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma</td>
<td>17%</td>
<td>24%</td>
<td>47%</td>
<td>53%</td>
<td>83%</td>
<td>61%</td>
<td>89%</td>
<td>17%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>40%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

PSA – Prostate Specific Antigen  
PSAP – Prostate Specific Acid Phosphatase  
CK – Cytokeratin  
AR – Androgen Receptor  
TTF – Thyroid Transcription Factor  
CD – Cluster of differentiation  
Chrom A – Chromogranin  
Synap - Synaptophysin
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