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Squamous Cell Carcinoma of the Prostate Gland: A Review of the Literature

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Abstract

Primary squamous cell carcinoma of the prostate (PSCCP) is rare; in view of this practitioners may be un-familiar with its diagnosis and biological behavior. Patients with PSCCP may present with lower urinary tract symptoms, haematospermia, haematuria, epididymoorchitis, abnormal feeling prostate on rectal examination, symptoms of bony metastasis or its diagnosis, may be incidentally made as a histological finding from a prostatectomy specimen or prostate biopsy specimen. Rectal examination may reveal benign feeling or hard prostate or nodule in prostate. Diagnosis is based upon microscopic examination of the prostate which tends to exhibit infiltrating nests, strands, and sheets of polygonal cells which have nuclear atypia; Squamous differentiation in squamous cell carcinoma of prostate is manifested as individual cell keratinization, inter-cellular bridges or formation of keratin pearl; Negative staining for prostate specific antigen (PSA) and prostatic serum acid phosphatase (PSAP) on immunohistochemistry; microscopy confirmation of absence of adenocarcinoma in tumor; no previous history of hormonal treatment or radiotherapy to prostate, clinical and radiological evidence of absence of squamous cell carcinoma elsewhere. Various treatments options have been used including surgery, radiotherapy and chemotherapy with variable degrees of success but most often with short periods of survival and anecdotal findings of longer survival but on the whole a multi-modal treatment approach would appear to be associated with longer term survival in few reported cases but consensus opinion on treatment does not exist in view of the rarity of the disease. PSCCP is rare and consensus opinion does not exist with regard to the best treatment option but multi-modal treatment may perhaps be most beneficial. Cases of PSCCP should globally be entered into a multi-center trial in order to determine the best treatment option that would improve upon the prognosis of this aggressive tumour which is currently associated with poor prognosis and aggressive behavior.

Key Words: Primary squamous cell carcinoma of prostate; PSA; PSAP; Radiotherapy; chemo-radiation; chemotherapy

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Introduction

Squamous cell carcinoma of the prostate is a rare clinical entity in view of which most clinicians would be unfamiliar with its biological behavior and treatment. The ensuing paper has been divided into (A) which contains an overview of squamous cell carcinoma of the prostate gland and (B) which contains miscellaneous narrations and discussions from some reported cases.

Methods

Various internet data bases were searched using the following search words: Primary Squamous cell carcinoma of prostate; metastatic squamous cell carcinoma of the prostate. Information obtained from 27 references was used for the review article.

Literature Review

(A) Overview - Genreal

Squamous cell carcinoma of the prostate gland is rare with an incidence of less than 0.6% of all prostate cancers. [1]

The criteria for diagnosing primary squamous cell carcinoma of the prostate include:

- Presence of unequivocal characteristics of malignancy
- Presence of definitive squamous differentiation on microscopic examination
- Lack of a conventional adenocarcinoma component on microscopic examination
- The patient should not have had any previous treatment with radiotherapy or hormonal treatment
- There should not be any squamous cell carcinoma elsewhere. [1] [2]

Clinical characteristics of primary squamous cell carcinoma of prostate

- Primary squamous cell carcinoma of the prostate is believed to originate from the peri-urethral glands or acinar basal cells of the prostate. [1]
- Primary squamous cell carcinoma is believed to develop de novo or following estrogen therapy, treatment with flutamide, radiation seed implantation.
- Primary squamous cell carcinoma of the prostate gland is associated with poor survival of patients. [1]
- Patients with primary squamous cell carcinoma of the prostate tend to have normal serum PSA and PSAP levels [1]
- Patients with primary squamous cell carcinoma of prostate tend to develop osteolytic metastases. [1]
- Patients with primary squamous cell carcinoma of prostate do not respond to hormonal treatment [1]
- Patients with primary squamous cell carcinoma of prostate do not develop elevation of serum levels of PSA with metastases [1]

Histogenesis

- Squamous cell carcinoma of the prostate is a very rare and is said to have an incidence of 0.6-1% of all prostatic malignancies. [3]
- There is no consensus opinion regarding its aetiology.
- In about 50% of cases of squamous cell carcinoma of prostate, it arises in the settings of previous radiotherapy or hormonal treatment for adenocarcinoma of prostate; nevertheless, it also occurs in the absence of previous treatment as a de novo carcinoma. [3]
- There has been the belief that the squamous component emanates from squamous metaplasia of acini and ductal elements [3]
- Microscopic examination frequently reveals non-neoplastic squamous metaplasia in the prostate gland which had been associated with chronic inflammation or infarction. Furthermore, malignancies such as hormonal or radiotherapy-treated adenocarcinoma of prostate or urothelial carcinoma could exhibit squamous metaplasia. [3]
- It has been postulated that squamous cell carcinoma of the prostate could be derived from pluripotent stem cells that are capable of multi-directional differentiation. [3]

Age range

- Malik et al, [4] stated that the ages of patients in their review of a series of 22 reported cases of primary squamous cell carcinoma of prostate had ranged from 42 years to 85 years
- Alva and Das [3] had observed from their review of the literature that the average age of onset of symptoms in patients with squamous cell carcinoma of the prostate gland was 68 years and the ages had ranged between 42 years and 86 years. They had also found that in the case of patients where the squamous cell carcinoma had ensued radiotherapy or hormonal treatment for adenocarcinoma of prostate, the time elapsed had varied from 3 months to 10 years.

Presentation

- Patients with PSCCP ranged in age from 42 to 85 years with presenting symptoms including LUTS, acute urinary retention, urinary tract infection, hematuria, and bony pain secondary to metastases. A total of 56% of patients were found to have metastases to varying locations including bone, lungs, liver, and lymph nodes with survival ranging from 0 to 60 months with an average survival of 11.9 months.
- Alva and Das [3] stated that irrespective of its origin, the symptoms of squamous cell carcinoma of the prostate tend to be those of prostatism as a result of bladder outlet obstruction.

Patients with primary squamous cell carcinoma of the prostate gland may present with the following symptoms:

- Lower urinary tract symptoms including urinary frequency, dysuria, obstructive symptoms (poor flow, intermittent and hesitancy) [4]
- Haematospermia [4]
- Signs and symptoms of epididymoorchitis [4]
- Haematuria [4]

- Evidence of bony metastasis investigation of which leads to the diagnosis [4]

In a review of 22 previously reported cases of primary squamous cell carcinoma of prostate, Malik et al. [4] found that the presenting symptoms included lower urinary tract symptoms, acute urinary retention, haematuria, and bone pain resulting from metastases. They also found that a total of 56% of the patients had metastases in various locations which included bone, lungs, liver, and lymph nodes.

Clinical examination findings in primary squamous cell carcinoma of prostate may include:

- Benign feeling prostatic enlargement
- Nodule in prostate which may be non-tender or tender

Radiological findings: Computed tomography (CT) scan, PET scan, Magnetic Resonance Imaging (MRI) scan, ultrasound scan, trans-rectal ultrasound scan, Isotope bone scan (see figures 1 and 2).

- Trans-rectal ultra-sound scan of prostate gland is used to study the characteristics of the prostate gland to determine the echogenicity of the gland and to identify any abnormal looking areas within the prostate as well as if the lesion in the prostate gland has involved the seminal vesicle, ejaculatory duct or if the lesion has extended beyond the capsule of the prostate or if it has involved the base of the urinary bladder.
- Trans-rectal ultra-sound scan of the prostate is a useful way to obtain biopsies from various areas of the prostate gland as well as any abnormal looking areas of the prostate gland for histological examination.

Ultrasound scan and CT scan in primary squamous cell carcinoma of prostate may show:

- Thick walled urinary bladder [4]
- A mass in the prostate gland
- Ultrasound scan, CT scan and MRI scan would demonstrate absence of a tumour mass in the pelvis, abdomen and thorax as well as elsewhere in the body which would indicate that the lesion is a primary prostatic lesion

Diagnosis

Diagnosis of primary squamous cell carcinoma should be based upon the characteristic findings of biopsy specimens of the prostate or prostatectomy specimens (trans-urethral resection specimen of the prostate and also this could be found in an open prostatectomy specimen).

Microscopic features (see figures 3 and 4 which also include immunohistochemistry)

Pure squamous cell carcinoma tumours of the prostate on microscopic examination tend to exhibit infiltrating nests, strands, and sheets of polygonal cells which have nuclear atypia. [1]

Squamous differentiation in squamous cell carcinoma of prostate is manifested as individual cell keratinization, inter-cellular bridges or formation of keratin pearl [1].

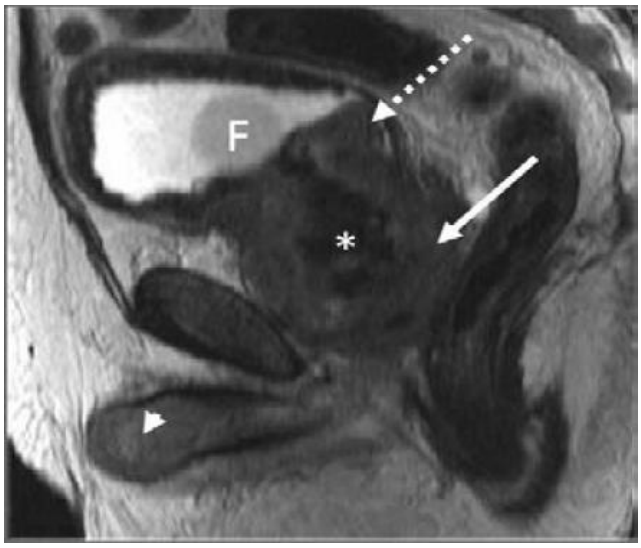

Figure 1: Sagittal turbo spin-echo T2-weighted magnetic resonance image demonstrates a T2-hypointense soft tissue mass replacing the entire prostate (solid arrow) with central necrosis (asterik) and extension into the bladder base (dashed arrow). There is a Foley catheter (F) within the urinary bladder. Penile soft tissue mass (white arrow head) is better demonstrated in figure 2. Reproduced from: [4] Malik D R, Dakwar G, Hardee M E, Sanfilippo N J, Rosenkrantz A B, Taneja S S. Squamous Cell Carcinoma of the Prostate Rev. Urol. 2011; 13(1): 56 – 60 Copyright © 2011, Med Reviews, LLC under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Immunohistochemical staining (see figure 2)

Negative stains

Primary squamous cell carcinomas of prostate gland stain negatively for:

- PSA [1]
- PSAP [1]

Molecular genetic studies

Molecular genetic studies had shown that squamous malignant cells could either be diploid in a case of adenosquamous carcinoma with well differentiated squamous component which was reported by Devaney et al, [5] and aneuploidy or tetraploid as reported in a case with moderately dedifferentiated squamous component by Bassler et al. [6] It has been suggested that this disparity would perhaps be related to the degree of differentiation [3].

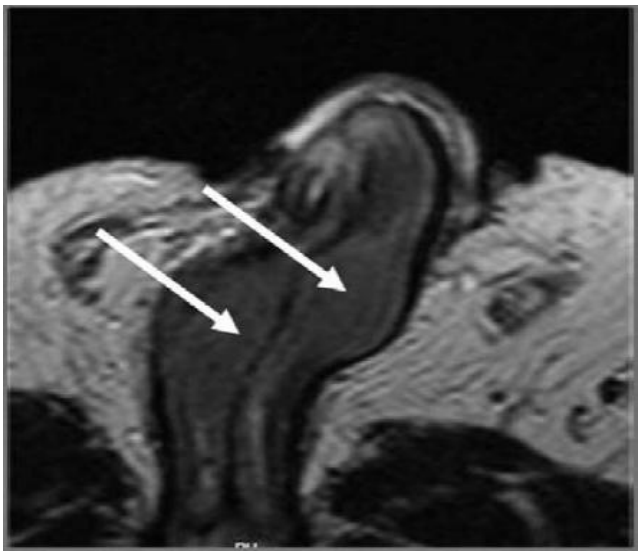

Figure 2: Axial turbo-spin echo T2-weighted magnetic resonance image demonstrates well-circumscribed T2-hypointense soft tissue masses (solid arrows) within both corpora cavernosa, consistent with penile metastases. Reproduced from: [4] Malik D R, Dakwar G, Hardee M E, Sanfilippo N J, Rosenkrantz A B, Taneja S S. Squamous Cell Carcinoma of the Prostate Rev. Urol. 2011; 13(1): 56 – 60 Copyright © 2011, MedReviews, LLC under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Differential Diagnosis

Primary squamous cell carcinoma of the prostate is rare in view of this anytime anytime a patient is diagnosed as having squamous cell carcinoma of prostate clinicians should make sure that a thorough diagnostic work up is done to exclude a primary squamous cell carcinoma elsewhere metastasizing to the prostate.

Treatment and Outcome

In a review of 22 previously reported cases of primary squamous cell carcinoma of prostate, Malik et al. [4] found that the survival of the patients had ranged from 0 to 60 months and the average survival was 11.9 months.

Moskovitz et al. [7] earlier on in 1993 stated that the average survival time had been estimated to be 14 months.

In 1953, Thompson et al. [8] reported that 5 out of 7 patients in their case series with squamous cell carcinoma of the prostate had survived less than one year.

With regard to primary pure squamous cell carcinoma of the prostate gland, there is scarcity of information regarding the best treatment modality.

Munoz et al. [9] had stated that there is the feasibility that at least some localized tumours could be resected with similar modalities to comparably staged adenocarcinoma of the prostate gland and that long term survivors had been reported by some authors in this setting [8] [10] [11] [12].

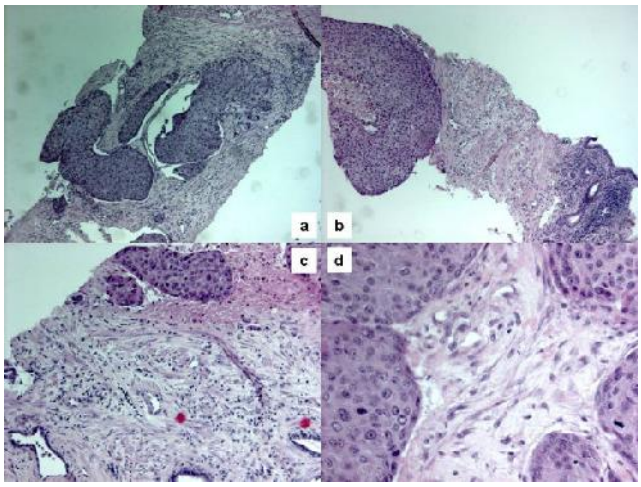

Figure 3: Haematoxylin and eosin-stained sections showing solid sheets of squamous cells infiltrating the right lobe of the prostate (a; original magnification 10 x) and the left lobe (b, c: original magnification 10 x and 20 x, respectively). Mytotic activity may also be observed (d; original magnification 40 x). Reproduced from: Munoz F, Franco P, Ciammella P, Clerico M, Giudici M, Filippi A R, Ricardi U. Squamous cell carcinoma of the prostate: long-term survival after combined chemo-radiation. Radiation Oncology 2007; 2: 15 Published on line 2007 Apr 3 DOI: 10.1186/1748-717X-2-15 © Munoz et al; licensee BioMed Central Ltd. This is an open access article distributed under the creative Commons Attribution License (httpp://creativecommons.org/licenses/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Little et al. [10] reported 2 patients who had undergone an aggressive surgical treatment in the form of cysto-prostatectomy and bilateral pelvic lymphadenectomy and additional total urethrectomy to ensure negative distal urethral margins as treatment for squamous cell carcinoma of prostate. They reported that one patient remained free from disease at 40 months following the initial diagnosis and the second patient had died of lung metastases 25 months following the initial presentation. Gray et al. [11] reported a patient with squamous cell carcinoma of prostate who had undergone trans-pubic radical cystoprostatectomy with complete urethrectomy and bilateral pelvic lymph node dissection. The pubic symphysis was excised in the operation and an abdominoperineal resection of the rectum was also undertaken with construction of a sigmoid colostomy. They reported that the patient had died 6 months post-operatively of perineal recurrence.

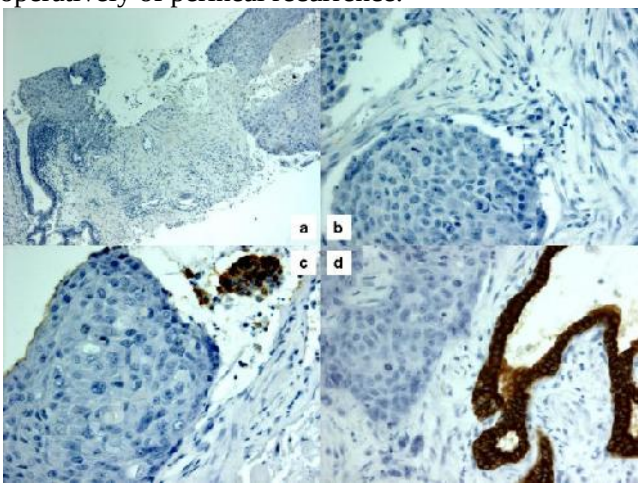

Figure 4: Immunohistochemistry showed negativity to cytokeratin 7 (a; original magnification 10 x) and cytokeratin 20 (b; original magnification x 40 x). Squamous carcinoma cells also stained negative for PSA and PAP, while adjacent remaining glands stained positive (c, d; original magnification 40 x). Reproduced from: Munoz F, Franco P, Ciammella P, Clerico M, Giudici M, Filippi A R, Ricardi U. Squamous cell carcinoma of the prostate: long-term survival after combined chemo-radiation. Radiation Oncology 2007; 2: 15 Published on line 2007 Apr 3 DOI: 10.1186/1748-717X-2-15 © Munoz et al; licensee BioMed Central Ltd. This is an open access article distributed under the creative Commons Attribution License (httpp://creativecommons.org/licenses/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In view of the rarity of primary squamous cell carcinoma of prostate, there is no consensus opinion regarding the best treatment modality. Nevertheless, surgical treatment and multi-modal approach have been used most often with varying success [4]. Munoz et al. [9] stated that as far as response to treatment is concerned, squamous cell carcinoma of the prostate is on the whole refractory to hormonal manipulation, but few cases of squamous cell carcinoma of the prostate might be susceptible to chemotherapy and radiotherapy and that numerous drugs have been employed, which have been mainly based upon the experience with epithelial tumours located in other anatomical sites. They also stated that DDP-based regimens are the most established ones, possibly combined with bleomycin (BLM), peplomycin (PEP) and methotrexate (MXT). They further stated that chemotherapy may be used as a single agent in a metastatic disease setting or in a combined modality approach, especially in locally advanced disease.

In 2007, Munoz et al. [9] reported a survival rate of 60 months following a multi-modal treatment approach in a 76-years-old man who had presented with extra-capsular primary squamous cell carcinoma of prostate. He received three courses of chemotherapy with cisplatin (CDDP), on day 1 and continuous infusion with 5-fluorouracil (5-FU), on days 1 to 5. This treatment was followed by a full course of radiotherapy to the pelvis with a boost dose to the prostatic bed and the prostate gland.
In 2000, Imamura et al. [13] reported a patient with squamous cell carcinoma of the prostate who had undergone cystoprostatectomy followed by adjuvant chemotherapy using methetrexate (MTX), peplomycin (PEP), and CDDP regimen who had survived for 60 months.

Uchibachi et al. [14] reported a patient with organ-confined squamous cell carcinoma of the prostate who had received multi-modal therapy which included radiotherapy to his pelvis and intravenous administration of bleomycin and intra-arterial administration of CDDP. The patient at the time of publication of the paper had survived for 21 months.

Corder and Cicmil [15] reported a patient with squamous cell carcinoma of the prostate with pulmonary metastases they had treated with administration of adriamycin 20 mg/m2 daily for 3 days, in 21-days cycles, in which marked regression

of pulmonary nodes was achieved. They reported that the tumour response had lasted 5 months.

Majeed et al. [16] reported an 18 month disease free survival in a patient who had undergone multi-modal treatment. The patient had undergone radical retro-pubic prostatectomy, bilateral pelvic lymphadenectomy with evidence of positive surgical margins and this was followed by six cycles of combination chemotherapy which included mitoxantrone, CDDP, and external beam radiotherapy to the bed of the prostate gland.

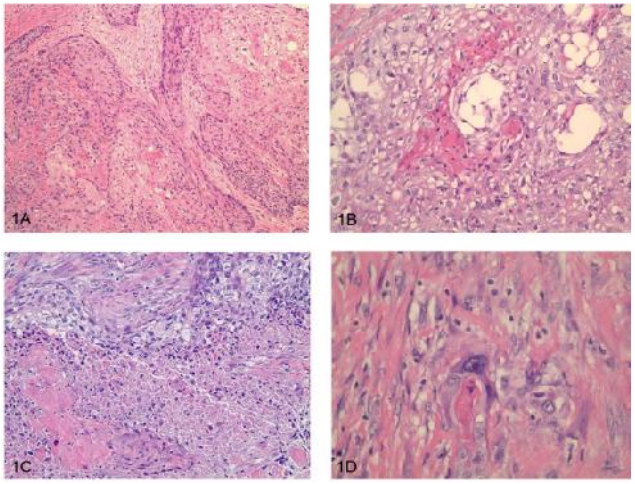

Figure 5: 1A) Infiltrating tumour mass forming nests and cords1B) Large, cohesive cells, with abundant glassy eosinophilic cytoplasm and well defined cell borders; focal keratinizing. 1C) Focal tumour necrosis 1D Poorly-differentiated cells with high grade nuclei infiltrating into stroma. Reproduced from: [3] Arva N C, Das K. Diagnostic dilemmas of squamous differentiation in prostate carcinoma case report and review of the literature Diagnostic Pathology 2011 May 31; 6: 46. Doi: 10.1186/1746-1596-6-46. www.diagnosticpathology.org.content under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

Okada and Kamizaki [17], reported a patient with T3N1M0 squamous cell carcinoma of prostate who was treated by radiotherapy to the pelvis and a boost radiotherapy to the prostate as well as two cycles of chemotherapy which had consisted of an intravenous injection of PEP, 15 mg, weekly up to 150 mg, and CDDP, 80 mg/m2, every fourth week. Okada and Kamizaki, [17] reported that the patient had had an 18 month disease free survival at the time of the report of their case.

With regard to surgical treatment alone, Little et al, [10] reported a 40-month and 25-month survival in two patients. The first patient, who had survived for 40 months at the time of their report, had organ-confined disease and the second patient had squamous cell carcinoma of the prostate with lymph node involvement. Both patients had undergone aggressive surgical treatment which had included radical cystoprostatectomy and bilateral lymphadenectomy. The first patient who had organ confined disease had also undergone total urethrectomy and ileal conduit urinary diversion and the second patient who had metastatic disease had had Kock pouch urinary diversion.

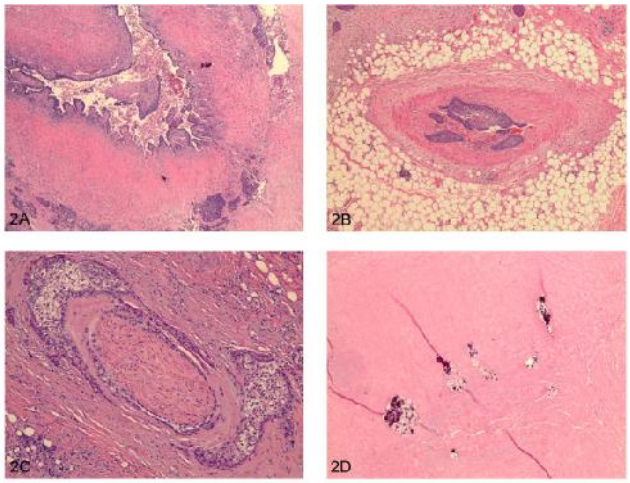

Figure 6: 6A Tumour extending into seminal vesicles; 6B Lymphovascular invasion; 6C Perineural invasion; 6D Areas of necrosis with calcifications consistent with therapy effect. Reproduced from: [3] Arva N C, Das K. Diagnostic dilemmas of squamous differentiation in prostate carcinoma case report and review of the literature Diagnostic Pathology 2011 May 31; 6: 46. Doi: 10.1186/1746-1596-6-46. www.diagnosticpathology.org.content under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

With regard to radiotherapy alone in the treatment of squamous cell carcinoma of the prostate, there is paucity of experience. However, some observations had been documented in relation to the use of radiotherapy in this disease and these include: (a) Moyana [18] had postulated that squamous cell carcinoma of the prostate gland emanates from metaplastic foci following radiotherapy; (b) Mott [19] had reported one case in which a patient who had an osteolytic lesion in his right femur and who had been

treated with cobalt radiotherapy to the pelvis and femur had survived for 8 months following his presentation at the time of publication of the paper; (c) Munoz et al. [9] had reported a review of reported cases and concluded that radiotherapy alone as a curative treatment for early-stage squamous cell carcinoma of the prostate was only investigational; (d) Malik et al. [4] had stated that in the case of locally advanced and metastatic squamous cell carcinoma of prostate, radiotherapy could be beneficial as part of a multi-modal approach and that guidelines for radiotherapy doses could be extrapolated from squamous cell carcinomas from other anatomic sites which have similar behavior patterns for example head and neck squamous cell carcinoma.

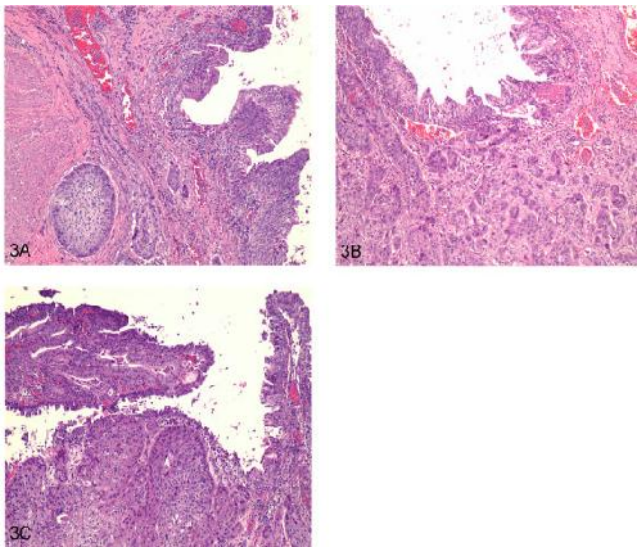

Figure 7: 7A) Hyperplastic urothelium with focal frond-like proliferation. The urothelial cells were slightly enlarged but the nuclear to cytoplasmic ratio was maintained and the nuclear polarity was preserved. 7B) Squamous cell carcinoma infiltrating lamina propria and detrusor muscle 7C) Squamous cell carcinoma extending, focally, into the urothelial mucosa Reproduced from: [3] Arva N C, Das K. Diagnostic dilemmas of squamous differentiation in prostate carcinoma case report and review of the literature Diagnostic Pathology 2011 May 31; 6: 46. Doi: 10.1186/1746-1596-6-46. www.diagnosticpathology.org.content under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

Sieracki et al. [20] reported one patient with squamous cell carcinoma of prostate who was treated by radiotherapy and who had survived almost 9 years. With regard to local excision, Masuda et al. [12] reported a patient who had a tiny sub-urethral squamous cell carcinoma of the prostate and who had remained free of recurrence for 6 years following local excision.

(B) Miscellaneous narrations and discussions from some reported cases

Malik et al. [4] reported a 77-year-old man with a past history of chronic lymphocytic leukemia (CLL) who had previously presented with haematospermia and who was treated with antibiotics for epididymoorchitis with complete resolution. He subsequently developed lower urinary react symptoms and digital rectal examination revealed a benign prostatic hypertrophy. His serum prostate specific antigen (PSA) was normal. He had CT scan of abdomen and pelvis which showed a uniformly thickened urinary bladder wall. He next underwent transurethral microwave thermotherapy with minimal relief of his symptoms. He later on, developed visible haematuria which required catheterization and bladder irrigation with a 3-way catheter and blood transfusion. He had another rectal examination which revealed a firm prostate suggestive of a carcinoma. He also had cystoscopy which showed indentation of the bulbar urethra, but the view of the bladder was not good enough to rule out a urinary bladder lesion. He underwent trans-rectal ultrasound scan guided biopsy of the prostate and histological examination of the specimen revealed anaplastic squamous cell carcinoma in multiple cores. He had a further CT scan of thorax, abdomen and pelvis which had shown multiple enlarged lymph nodes throughout the retroperitoneum, small pulmonary nodules, (these were thought to be due to the CLL), a low-attenuation region in the right central prostate gland which was considered to likely represent necrosis from microwave therapy, posterior lateral extension of the prostate gland, and two nodules along the penile shaft which were adjudged to be likely in the corpus cavernosum. He had another cystoscopy which revealed a normal bladder and urethral indentation due to compression by the palpable nodule. The prostate was noted to be vascular with luminal necrosis. He next had MRI scan of the pelvis which showed a large infiltrative neoplasm which had replaced the prostate with invasion of the urinary bladder base and left seminal vesicle with areas of necrosis and haemorrhage (see figure 1). Soft tissue deposits were also seen near the glans penis and there was extensive pelvic lymph adenopathy, as well as right iliac wing and right sacral osseous metastasis

(see figure 2). He next had positron emission tomography (PET) scan which did show markedly increased fluorodeoxyglucose (FDG) uptake in the base of the penis, extensive FDG uptake throughout the prostate gland and this had extended and involved the bladder, numerous FDG avid pulmonary foci, increased metabolic uptake in the base in T12, sacrum, right iliac bone which were consistent bony metastases. There was also diffusely increased uptake in the right bicep muscle. MRI scan of the brain did not show any metastasis. In view of the extent of the disease, he received palliative radiotherapy and after he had completed the radiotherapy treatment he died (3 months after his initial presentation). Malik et al. [4] stated the following:

- There is no definitive consensus opinion treatment for squamous cell carcinoma of the prostate gland but various treatment options have been used including surgical intervention, chemotherapy, and radiotherapy without durable response. Nevertheless, multi-modal treatments would appear to be the most promising with longer duration of survival.
- Mott et al. [19] described the first accepted criterion for the definition of primary squamous cell carcinoma of the prostate which include: (a) a clearly malignant neoplasm as judged by invasion, disordered growth, and cellular anaplasia; (b) definitive squamous features of keratinization, squamous pearls, and / or many distinct intercellular bridges; (c) lack of any glandular or acinar pattern; (d) no previous estrogen treatment; and (e) the absence of primary squamous cell carcinoma elsewhere, particularly in the urinary bladder. [19]
- The aforementioned criteria are pivotal to the differentiation between primary squamous cell carcinoma and non-neoplastic squamous metaplasia which can occur following infarct, acute/chronic prostatitis, granulomatous-prostatitis due to Bacillus Calmette-Guérin, estrogen treatment, or radiotherapy. [7] [21]
- With regard to the histogenesis of primary squamous cell carcinoma of the prostate, Thompson et al. [8] are of the opinion that primary squamous cell carcinoma of the prostate originates from the urothelium of the prostatic urethra, but Gray and Marshall [11] had suggested that it originates from the transitional epithelium of per-urethral ducts. Furthermore, Sieracki [20] is of the view that that squamous cell carcinoma of prostate originate from the basal cells of prostatic acini and Lager et al. [22] postulated that squamous cell carcinoma developed as a sequel of adverse stimuli affecting columnar cells which cause them to lose their ability to produce prostate specific antigen (PSA) and prostatic specific acid phosphatase (PAP), even though retaining the ability to produce keratin.
- Typically squamous cell carcinoma of the prostate does not result in elevation of levels of PSA or PAP.
- Mott [19] had stated that bony metastases in squamous cell carcinoma of prostate tend to exhibit osteolytic rather than the osteoblastic appearance seen in adenocarcinoma of prostate.

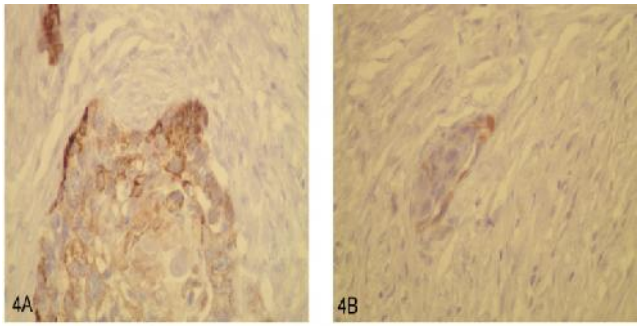

Figure 8: 8A) Viable neoplastic cells staining positive for AMACR. 8B Endothelial cells in the vessels adjacent to the tumour showing focal nuclear AMACR positivity. Reproduced from: [3] Arva N C, Das K. Diagnostic dilemmas of squamous differentiation in prostate carcinoma case report and review of the literature Diagnostic Pathology 2011 May 31; 6: 46. Doi:10.1186/1746-1596-6-46. www.diagnosticpathology.org.content under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

Munoz et al. [9] reported a 76-year-old man who had pure squamous cell carcinoma of the prostate, who was admitted and catheterized because of acute retention of urine and who had had voiding symptoms for two months. He had rectal examination which revealed an unevenly swollen and enlarged prostate gland of stony-hard consistency, with an irregular capsule. His serum PSA and PAP levels were within normal range. He had trans-rectal ultrasound scan which had shown hypo-echoic lesions in the left peripheral zone of the prostate gland. He had excretory urogram, urine cytology and urethro-cystoscopy which were negative for malignancy and his bladder neck, was noted to be

slightly elevated. He had a computed tomography (CT) scan of the abdomen which revealed an irregularly enlarged prostate with a peripheral hypo-dense mass within, compressing the base of the bladder and disrupting the anatomy of the prostate. There was no evidence of lymph node enlargement anywhere in the abdomen. He had magnetic resonance imaging (MRI) scan which did not demonstrate clarity in the boundary between the transition zone and the peripheral zone. It demonstrated that the signal intensity had decreased in the left peripheral zone on T2-weighted images and extra-capsular disease was shown in at least 2 sites of the prostatic profile. There was no evidence of bony metastasis in a total body bone scan which he had. He next had sextant trans-rectal ultrasound-guided needle biopsy of prostate and histological examination of the specimen had shown nests and sheets of moderately differentiated squamous carcinoma cells which were characterized by intercellular bridges. The examination also showed focal areas with evidence of keratin pearl formation, and it did not show any squamous metaplasia or transitional cell or adenocarcinomatous components. Immunohistochemical examination of the specimen showed that the squamous cell carcinoma of prostate component was negatively stained for PSA, PAP and cytokeratin 7 and 20, but it stained positively for high molecular weight cytokeratin (see figures 3 and 4). Based upon a combination of the clinical, pathology and radiological findings a diagnosis of AJCC-UICC Stage III (cT3aN0M0) pure primary squamous cell carcinoma of the prostate was made. He was treated by means of combined-modality treatment, with the administration of 3 course cisplatin 75 mg/m^2 on day 1 and continuous infusion of 5-fluorouracil 750 mg/m2 on day 1 to 5. He subsequently received radiotherapy with a total dose of 46 Gy to the whole pelvis, with further boost doses of 20 Gy to the bed of the prostate gland as well as adjuvant 6 Gy to the prostate gland which totalled 72 Gy. He remained free of disease for 5 years, but finally he experienced local relapse and subsequently died of acute renal failure which had ensued bilateral hydro-uretero-nephrosis. Munoz et al. [9] made the following conclusions: It had remained questionable which treatment modality would be the most appropriate therapeutic approach for pure squamous cell carcinoma of the prostate gland; their report had demonstrated that a prolonged disease control, with a consistent survival time, could be achieved by the combination of effective local treatment such as radiotherapy with systemic infusion of chemotherapeutic drugs.

Arva and Das [3] reported a 77-year-old man who had previously undergone brachytherapy for prostate cancer 10 years earlier. He had also one year prior to his presentation undergone trans-urethral resection of prostate for urinary obstruction which had been complicated by urinary tract infections. He was admitted as a result of decreased urine output and acute kidney injury and metabolic acidosis. His serum creatinine was 10 mg/dl. He had computed tomography scan of abdomen which had demonstrated bilateral grade 2 hydro-ureteronephrosis with the obstruction at the level of the vesico-ureteric junction for which he underwent insertion of percutaneous nephrostomies bilaterally. He next had a cystourethrogram which had shown a colo-urethral fistula in the area of the prostatic urethra and this had extended to the rectum. The bladder wall was thickened but its lumen was small and irregular. He underwent cystoprostatectomy, construction of ileal conduit and repair of the recto-urethral fistula. Macroscopic examination of the cystoprostatectomy specimen revealed that the entire prostate gland had been replaced by a white firm irregular tumour mass and the urinary bladder mucosa was very congested and looked irregular and there was no evidence of mucosal growth or luminal masses. The thickness of the wall of the urinary bladder varied from 0.5 cm to 1.0 cm. Microscopic examination of the prostate revealed an infiltrating tumour mass which had formed nests and cords (see figure 5A). There was no evidence of benign prostatic glands seen in the specimen. Cytological examination of the specimens showed that the cells were large, cohesive, and exhibited abundant glassy eosinophilic cytoplasm and well-defined borders. Keratinization was observed (see figure 5B). The tumour exhibited focal necrosis (see figure 5C) and areas of the tumour were seen that had less differentiated cells with high grade nuclei which had infiltrated singly into the stroma (see figure 5D). The morphological characteristics of the tumour were adjudged to be compatible with poorly differentiated squamous cell carcinoma. There was no evidence of any other differentiation including adenocarcinoma or urothelial carcinoma. Microscopic examination had also shown that the tumour had replaced the whole prostate and had extended into the seminal vesicles, peri-prostatic and peri-vesical soft tissue (see figure 6A). The examination had also shown lymphovascular (see figure 6B) and peri-neural

invasion (see figure 6C) and it also showed areas of necrosis with calcifications which was adjudged to be consistent with therapy effect [6D]. Microscopic examination of the bladder wall sections showed inflamed and mostly denuded mucosa with underlying granulation tissue. In areas that had urothelium, the urothelium was hyperplastic and had focal frond-like proliferation. The urothelial cells were noted cytologically to be slightly enlarged and the nuclear cytoplasmic ratio was maintained and as well the nuclear polarity was preserved (see 7A). The degree of atypia was less than that observed in the tumour cells and was adjudged to represent reactive changes, pursuant to the inflammatory process. Areas of high-grade carcinoma were not seen. The lamina propria and the detrusor muscle of the urinary bladder were noted to have been infiltrated by the squamous cell carcinoma (see figure 7B) which had also extended, focally, into the urothelial mucosa (see figure 7C). Immunohistochemical studies had also been undertaken which had shown that viable neoplastic cells had stained positive for racemace/AMACR (see figure 8A) and negative for prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), prostate specific acid phosphatase (PSAP) and P5501S (553-amino acid protein that is localized to the Golgi complex and expressed in both benign and neoplastic prostate tissues). It was also noted that AMACR had also stained the cells within the vessels that were adjacent to the tumour (see figure 8B). Based upon the aforementioned findings a final diagnosis of squamous cell carcinoma involving the prostate and the urinary bladder was made. At that stage the question for the clinicians and the pathologist to answer was whether the squamous cell carcinoma had developed via divergent differentiation from adenocarcinoma of prostate following treatment, or it had developed from squamous differentiation of urothelial carcinoma, or it was a de novo second primary malignancy of the prostate gland.

Arva and Das [3] stated that they had identified in the English literature 66 cases of carcinoma of the prostate gland with squamous differentiation which they initially classified as either pure squamous cell carcinoma or adenosquamous carcinoma and furthermore they had subdivided each of the two categories of tumours into carcinomas developing de novo and carcinomas which had developed following a previous diagnosis of adenocarcinoma of the prostate. Arva and Das [3] further stated that their review of the literature had shown that the squamous component was associated with adenocarcinoma in 39 (60%) patients. Twenty seven patients had pure squamous cell carcinoma of the prostate. In approximately 50% of the patients, the squamous differentiation had developed in patients who had previously undergone treatment for adenocarcinoma of the prostate gland (35 patients). De novo squamous cell carcinoma of the prostate gland developed in the remaining 31 patients. With regard to the patients who had previously had adenocarcinoma of prostate, 28 patients had developed adenosquamous carcinoma and only 7 patients had developed pure squamous cell carcinoma of the prostate subsequently. Arva and Das [3] also found in their review that in majority the patients the diagnosis was made from biopsy specimens of the prostate or from trans-uretral resection of prostate specimens by adhering to the criteria set by Mott. [19] They had found out that with regard to the 33 cases of adenocarcinoma with squamous differentiation which Parwani et al. [23 had reported, there were 8 cases of pure squamous cell carcinoma of prostate (3 cases had occurred following treatment for adenocarcinoma and 5 de novo cases. Their review findings had confirmed that in order to exclude another urological primary malignancy, in all the aforementioned patients, cystoscopy was undertaken and furthermore in one case, cystoprostatectomy was performed and histological examination did show no evidence of urinary bladder tumour. In other cases reported by Nabi et al. [24], Mohan et al, [25] and Rahmanout et al. [26] another source of primary squamous cell carcinoma involving the prostate had been based upon a normal cystoscopy. Okada and Kamizaki [17], reported a patient who had undergone trans-urethral biopsy in which histological examination of the specimens excluded vesical or urethral malignancy. In another case reported by Sarma et al. [27] the diagnosis was made after cystoprostatectomy.

Alva and Das [3] found from their literature review that 35 patients who had had hormonal treatment or in addition radiotherapy for adenocarcinoma of prostate who had subsequently developed squamous component, 7 of them had developed pure squamous carcinoma (20%) and in the remaining 28 patients (80%) the squamous component was associated with classic adenocarcinoma (adenosquamous carcinoma). Alva and Das [3] were of the opinion that the bias would indicate that patients who have previously been

treated for pure adenocarcinoma of the prostate gland have a propensity for the development of squamous differentiation in association with adenocarcinoma and that the squamous component would perhaps represent divergent differentiation of the adenocarcinoma under treatment pressure rather than a second primary malignancy of the prostate gland.

Regardless of its origin, the symptoms of squamous cell carcinoma of the prostate are usually those of prostatism due to bladder outlet obstruction. The average age of onset is 68 years, ranging from 42 to 86. In those cases where the squamous carcinoma followed radiation or hormonal treatment for adenocarcinoma, the time elapsed varies from 3 months up to 10 years.

A final diagnosis of squamous cell carcinoma involving the prostate and urinary bladder was rendered. The question that arose was whether the squamous carcinoma developed through divergent differentiation from prostatic adenocarcinoma following treatment, represented squamous differentiation of a urothelial carcinoma, or it was the second primary prostatic malignancy in this patient.

Nabi et al. [24] reported 2 patients with primary squamous cell carcinoma of the prostate. They reported that one of the patients had presented with lower urinary tract symptoms and on rectal examination he was noted to have a hard nodular prostate. The second patient was admitted because of acute retention of urine and his rectal examination was noted to be normal (normal felling prostate gland). On evaluation both patients were found to have metastasis in the pelvis and right femur. Both patients underwent palliative trans-urethral resection of prostate and they also received chemotherapy (Adriamycin based). Nevertheless, both patients died at 4 months and 5 months of follow-up respectively.

Conclusions

PSCCP is a rare tumour, which accounts for 0.5% to 1% of all prostate carcinomas. The presenting symptoms range from lower urinary tract symptoms, haematospermia, haematuria, epididymoorchitis to bony metastases. It is typically regarded as an aggressive carcinoma which is associated with a median post-diagnosis survival of about 14 months. Clinically, prostatic squamous cell carcinoma remains characteristically different from its more common counterpart, prostate adenocarcinoma. Surgical treatment and multi-modal approaches are most commonly used, which had resulted in varying degrees of success. PSCCP is rare and consensus opinion does not exist with regard to the best treatment option. Surgical treatment and multimodal approaches are most commonly used, which had resulted in varying degrees of success but multi-modal treatment may perhaps be most beneficial. Cases of PSCCP should globally be entered into a multi-center trial in order to determine the best treatment option that would improve upon the prognosis of this aggressive tumour which is currently associated with poor prognosis and aggressive behavior.

Conflict of Interest: None

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