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Primary Signet-Ring Cell Carcinoma of the Prostate: A Review of the Literature

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Abstract
Primary and metastatic signet-ring-cell carcinoma of the prostate are rare, in view of this a number of clinicians may be unfamiliar with the disease entity. Both Primary and secondary metastatic signet-ring-cell carcinomas of the prostate (SRCCP) are rare and less than 200 cases of primary SRCCP have been reported. Primary SRCCP may be found incidentally; may present with lower urinary tract symptoms or just raised serum PSA levels; may present as mass/nodule in prostate; may be diagnosed in the investigation for primary cause of a metastasis. Diagnosis is based upon finding of adenocarcinoma of prostate with signet-ring cells on microscopic examination of prostate (usually high grade and more than 25% of signet-ring cells in tumour these days though previously 5 to 50% have been reported). Primary SRCCP stains positively with PSA and PAP. Diagnosis of primary SRCCP is established after excluding possible primary lesions elsewhere. Primary SRCCP can be treated by hormonal therapy, radiotherapy, surgery and chemotherapy but previous reports indicated poor prognosis with low-long term cancer-specific survival but a recent report had indicated an improved outcome but still the outcome for the younger age group was inferior. There is no consensus on the best treatment approach to further improve on prognosis. Primary SRCCPs tend to be high-grade/undifferentiated with poor prognosis; Recent data, had indicated improved survival but poor survival in younger patients. New cases of primary SRCCP should be entered into a multi-center trial to decide on the best treatment options and to find out if the prognosis would be influenced by the percentage of signet-ring cells. There is need to have a consensus opinion on the minimum proportion of signet-ring cells in a prostatic tumour that would constitute primary SRCCP.

Key Words: Primary signet-ring-cell carcinoma of prostate; PSA; PAP; PSAP, mucin; carcinoembryonic antigen; radiotherapy; hormonal therapy; chemotherapy; immunohistochemistry

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Introduction

Signet-ring-cell carcinoma of the prostate gland is rare. When a signet-ring-cell carcinoma is found in the prostate, both the pathologist and the urologist need to establish whether the signet-ring cell carcinoma involving the prostate is primarily of prostatic origin or it had developed as a metastatic lesion from a primary signet-ring-cell carcinoma elsewhere. The ensuing paper contains a review of the literature on primary signet-ring cell carcinoma of the prostate which has been divided into (A) an overview and (B) miscellaneous narrations from some reported cases of primary signet-ring-cell carcinomas and metastatic signet-ring cell carcinomas of the prostate.

Methods

Various internet data bases were searched including: google, google scholar, educus and PUB Med using the key words primary signet ring cell carcinoma of prostate, metastatic signet ring cell carcinoma of prostate, signet ring cell carcinoma of prostate. Information obtained from 31 references was used to write the review article.

Literature review

(A) Overview

- Signet ring carcinoma is rare and earlier report suggested in 2010 that less than 50 cases had been reported in the English literature [1]

- A Mayo clinic review in 2010 had identified only 9 cases (0.03%) in their institution between 1970 and 2008 and a PUB Med review had identified 42 cases [1]
- Reports gathered from case reports of signet ring carcinoma of the prostate indicate that the disease is highly malignant [2]

Definition: Primary signet-ring cell carcinoma of prostate is described as primary adenocarcinoma of the prostate with a prominent population of signet ring cells [3].

Diagnostic criteria (Stanford University Diagnostic criteria)

- There is no agreement on the percentage of signet ring cells in the tumour required for a diagnosis of primary signet-ring cell carcinoma of prostate. 5% to 50% have been described in the literature [3] but perhaps more than 25% signet ring cells may be the percentage to adopt.
- The nucleus is displaced and indented by clear mucin filled vacuole and the vacuole must be positive on mucin stain. It is worth noting that there are differential diagnoses to be excluded. Mucin-negative vacuolated "signet ring like" adenocarcinoma is more common. It had been suggested that perhaps mucin-negative vacuolated "signet ring like" adenocarcinoma might have been included in many studies, [3] and these mucin-negative vacuolated "signet ring like" adenocarcinomas are high grade also [3] and these mucin-negative vacuolated "signet ring like" adenocarcinomas tend to exhibit Gleason pattern 4, with ragged infiltration and poorly formed glands may simulate scattered signet-ring cells. [3] Cautery in TURP chips may cause stromal cell vacuoles [3]
- The infiltration patterns of signet-ring cell carcinoma of the prostate may vary from single to sheets of cells. [3] Signet ring-cell carcinoma of the prostate may rarely be associated with mucinous carcinoma. [3]
- The Gleason pattern of signet-ring cell carcinoma of prostate tends to be 5 definition but it may be associated with other patterns usually either Gleason 4 or 5 [3]
- Signet-ring cell carcinoma of the prostate gland tends to positively stained for prostate-specific antigen (PSA) and PAP [3]
- On the whole primary signet-ring cell carcinomas of the prostate tend to have poor response to therapy and poor prognosis [3]
- Clinicians need to exclude urothelial carcinomas involving the prostate gland and other non-prostatic origin tumours involving the prostate gland. [3] Mucinous urothelial carcinomas tend to be positive for HMWCK and doubly positive for CK7/20 in majority of cases. Mucinous urothelial carcinomas tend to be negative for PSA and PAP, [4] but some older reports had found some positivity [3] Gastro-intestinal tract carcinomas involving the prostate must also be differentiated from primary signet-ring cell carcinoma of the prostate. Gastro intestinal tract adenocarcinomas tend to be negatively stained on immunohistochemistry for PSA and PAP. Primary adenocarcinomas of the gastrointestinal tract tend to be positive on immunohistochemical staining with CDX2; however, it is worth noting that 30% of adenocarcinomas of the prostate stain positively with CDX2. [3] To confirm presence of a primary gastro-intestinal adenocarcinoma a good clinical history, gastrointestinal endoscopy and radiological imaging would be required. [3]

Presentation

- Raised levels of serum PSA: An asymptomatic person may be referred because of raised serum PSA level and upon biopsy of the prostate found to have signet-ring-cell carcinoma of prostate. The serum PSA may be slightly raised but in cases of metastatic or advanced cases the serum PSA could be quite high. Nevertheless, other patients may have serum PSA levels that are normal but they may have lower urinary tract symptoms and their investigation may lead to a diagnosis of primary signet-ring cell carcinoma.
- Lower urinary tract symptoms: Some patients may be referred because of lower urinary tract symptoms of diurnal urinary frequency, nocturia, poor urinary flow and their investigation may lead to a diagnosis of signet-ring cell carcinoma of prostate.
- Abnormal digital rectal examination finding on the prostate gland: Some patients may be found to have abnormal digital rectal examination in that the prostate gland may feel irregular, nodular, firm or hard and pathological examination of their prostate biopsy specimens may lead to the diagnosis of signet-ring-cell carcinoma of prostate. It is worth noting that some patients with signet-ring cell carcinoma of prostate may have benign feeling prostate gland.
- Urinary retention: Some patients who have been diagnosed as having urinary retention requiring catheterization upon investigation may be found to have signet-ring-cell carcinoma of prostate.
- Incidental finding in trans-urethral resection of prostate specimens or in open or laparoscopic prostatectomy specimens: Some patients may undergo (a) trans-urethral resection of prostate or open prostatectomy (trans-vesical or retro-pubic) under a

provisional diagnosis of benign prostatic hypertrophy, (b) Open radical or laparoscopic radical prostatectomy for carcinoma of the prostate, and pathological examination of the prostate may show signet-ring-cell adenocarcinoma of prostate.

- Incidental finding in the investigation of a metastasis. A patient may present with an enlarged lymph node for example an enlarged cervical lymph node which is considered to be a metastatic lymph node from an unknown primary tumour and digital examination may show an abnormality in the prostate gland and histological examination of which may lead to the diagnosis of signet-ring-cell carcinoma of the prostate. Another example is that investigation to find the primary cause of bone metastasis may result in the finding of a primary signet-ring-cell carcinoma of prostate.

Investigations

Generally in the assessment of every patient, full blood count, coagulation screen, serum urea and electrolytes, liver function tests, blood glucose, urinalysis, urine microscopy and urine culture are all basic tests to be carried out in the initial work out and assessment of the patient which do not directly diagnose signet-ring cell carcinoma of the prostate but are helpful. Some of the various investigations that are carried out in the assessment of a patient who has primary or metastatic signet ring cell carcinoma of the prostate gland are as follows:

- Serum PSA Serum PSA levels quite often are raised and they may be slightly raised but in cases of very advanced disease the levels may be quite high; however, perhaps in some tumours the serum PSA may not be raised. The serum PSA level of the patient is not diagnostic of signet-ring cell carcinoma of the prostate but if the levels are high then subsequent serum PSA levels could be used as one of the monitoring processes in the assessment of response to treatment.
- *Serum PSAP:* Serum Prostatic acid phosphatase levels may be raised but they would be non-specific and do not directly lead to a diagnosis of signet-ring-cell carcinoma of the prostate but if a diagnosis of signet-ring-cell carcinoma of prostate is made and the serum prostatic acid phosphatase level is raised then serum PSAP could also be used to monitor the progress of the patient.

Trans-rectal ultra-sound scan of prostate and biopsies

- Trans-rectal ultrasound scan of the prostate is used to assess the prostate gland to assess the prostate gland for homogeneity and to look for abnormal areas including hypo-echoic areas within the prostate gland. If any abnormal areas or lesions are found in the prostate gland, the location and size of the lesion(s) are assessed as well as whether or not the seminal vesicle or capsule of the prostate gland has been involved by the lesion. Trans-rectal ultrasound-guided biopsies are taken from the prostate gland inclusive of from any suspicious areas noted for pathological examination to establish diagnosis. Digital rectal examination is done preceding the procedure to assess the prostate gland and if any mass is found its characteristics are noted.

Trans-urethral and open prostatectomy

- Some patients undergo trans-urethral resection of prostate or open prostatectomy for various reasons and occasionally pathological examination of the specimen may show signet-ring cell carcinoma of the prostate which had not been suspected initially.

Ultra-sound scan of the renal tract, abdomen and pelvis

- Ultra-sound scan of the renal tract, abdomen and pelvis is usually done to assess the abdomen and renal tract which in some cases may show or exclude hydrouretero-nephrosis, any pelvic or abdominal masses. These scans would not establish diagnosis of signet-ring cell carcinoma but may show another lesion outside the prostate including enlarged lymph nodes or mass in the urinary bladder.

CT scan; PET – CT scan, and MRI scan

- Computed tomography (CT) scan, PET-CT scan, Magnetic Resonance Imaging (MRI) scans can be used to assess the prostate and prostatic lesion for its characteristics and also these radiological studies may be used to detect a lesion elsewhere within the body which in cases of primary signet-ring cell carcinoma of prostate may be metastases. At times when a diagnosis of signet-ring cell carcinoma of the prostate is made it is not clear initially whether the lesion is primary or metastatic and relevant radiological images may help find a primary lesion elsewhere. These radiological images can be used in the follow-up of patients to exclude metastasis or follow the progress of a metastatic lesion following treatment.

Isotope bone scan

Isotope bone scan is used to establish or exclude bone metastasis when a patient is found to have primary or metastatic signet-ring-cell carcinoma involving the prostate gland.

Chest X-ray: Chest X-ray can be undertaken to exclude or confirm presence of a metastatic lesion(s) in the lungs.

Macroscopic features

There have not been any specific macroscopic characteristic features of signet-ring –cell carcinoma of the prostate described to the knowledge of the

author which would make a clinician or pathologist suspect the possibility of signet-ring-cell carcinoma of prostate in the first instance without microscopic examination. Nevertheless, macroscopic examination of the tumour may reveal a grey-white looking tissue of the prostatic specimen.

Microscopic features

Histologically the tumour of the prostate is composed of 5% to 50% of signet ring cells due to the intracellular accumulation of mucin which had compressed the nucleus into a crescent shape. In addition to evidence of signet ring cells in the prostatic tumour, classic adenocarcinoma of the prostate is also present in the tumour [2]

- The typical microscopic features of signet-ring cell carcinoma of the prostate has been described as being primarily composed of tumour cells which exhibit signet ring patterns of which there must be at least 25% of the tumour cells having the signet ring pattern due to intracellular accumulation of mucin compressing the nucleus into a crescent shape. [2]
- The tumour tends to exhibit solid, acinar, single-line patterns. [2]

Immunohistochemistry (positive and negative stains)

Positive stains

The cytoplasmic vacuoles in signet-ring cell carcinomas of the prostate quite often stain positively with the following:

- PSA (variable degrees of positivity have been reported in some studies) [2]
- AE1/AE3 [2]
- CAM 5.2 [2]
- Ki-67 (mean 8%) [2]
- PAS-diastase [2]
- Mucicarmine (50%) [2]
- Alcian blue (60%) [2]
- A-methyl coenzyme A racemase (P503S) [2]
- Cytokeratin 5/6 [2]

Negative stains

Signet-ring cell carcinoma of prostate specimens, tend to stain negatively with:

- Bc12 (rare cells positive) [2]
- Carcinoembryonic antigen (CEA) (80%) [2]

Electron microscopic features

- Signet-ring cell carcinoma of the prostate specimens on electron microscopy tend to exhibit intracytoplasmic lumina lined by microvilli [2]

Upper and lower gastrointestinal endoscopy

- A number of times when a histopathological examination finding of signet-ring-cell carcinoma of prostate gland is made it may not be clear whether the carcinoma is primary or metastatic. In order to exclude a primary signet-ring-cell carcinoma of the upper and lower gastrointestinal tract, upper gastrointestinal and lower gastrointestinal endoscopies are undertaken and if any lesion is found biopsies are taken for histological examination.

Cystoscopy

Primary signet-ring-cell carcinoma of the urinary bladder may invade the prostate and it may be difficult to establish whether the lesion in the prostate is metastatic or primary. Cystoscopy is undertaken to exclude a urinary bladder lesion and if a lesion is found it can be removed by trans-urethral resection for histopathological examination and a bimanual examination of the urinary bladder is undertaken.

Differential diagnosis

Carcinomas of the prostate gland which on microscopic examination are seen to exhibit tumour cells with signet-rings may be primary signet ring carcinoma; however, it is worth noting that there are a number of pathologies involving the prostate gland which may mimic signet-ring cell carcinoma therefore attention to the detailed pathological characteristics of the specimen is required to establish a correct diagnosis. Some of the differential diagnoses include:

- Artifactual changes in lymphocytes within the prostate gland pursuant to trans-urethral resection of prostate (TURP) may mimic signet-ring cell carcinoma but microscopic examination in such cases would reveal no evidence of classic adenocarcinoma and on immunohistochemistry the specimens exhibit positive staining for CD45 and negative staining for PSA and negative staining for PAP [5]
- Benign signet-ring change in a benign prostate and in such cases microscopic examination would reveal no evidence of adenocarcinoma and immunohistochemistry examination of the specimens would show negative staining for mucin, PSA as well as negative staining for PAP. [6]
- Gastro-intestinal primary tumours metastasizing to the prostate gland are much more common and histological examination of the prostate would not in such cases reveal any typical features of adenocarcinoma of prostate. Furthermore gastrointestinal work-up by means of computed

tomography (CT) scan of abdomen, colonoscopy, and oesophago-gastroduodenoscopy would tend to reveal the primary tumour and histological examination of the gastrointestinal tract tumour would confirm the primary tumour. Additionally, immunohistochemistry of such lesions in the prostate tend to show negative staining for PSA and negative staining for PAP [2]

- Mucinous carcinoma with signet ring cells involving the prostate. In such mucinous carcinomas, greater than 25% of the tumour is extracellular mucin and less than 25% of the tumour cells exhibit signet rings. [2]

Treatment

Signet-ring cell carcinoma of the prostate gland so far has been treated by means of similar options of treatment which have been used to treat traditional adenocarcinoma of the prostate gland and these include: hormonal therapy, radiotherapy, and surgery as well as chemotherapy.

Outcome

Primary signet ring cell adenocarcinomas of the prostate had historically been described as aggressive tumours and up to 75% of such tumours had presented with locally-advanced disease at the time of diagnosis. [7] Nevertheless, it has been stated by Pernick and Thakore [7] that perhaps the figures may have been lower recently as a result of serum PSA testing and early detection of prostate cancer. A five-year cancer specific survival of 84% has recently been reported with improved results in recent cases [8].

(B) Discussion and miscellaneous narrations from some reported cases

Warner et al [1] identified nine patients who had been treated with primary signet ring cell carcinoma among 29,783 cases of prostate cancer that had been evaluated in Mayo Clinic from January 15, 1970, until January 2009. They reported that they had searched the English-language literature which had been published from January 1, 1980, to January 1, 2010, using the key words signet ring cell and prostate and they had found 42 cases. They stated that they had reviewed the 42 cases along with the additional 9 reported cases and evaluated the clinical characteristics, histological diagnosis, treatment modalities, and outcome following treatment. Warner et al. [1] reported that the ages of the patients ranged from 50 years to 85 years with a mean age at diagnosis of 68 years; the prostate-specific antigen (PSA) level ranged from 1.9 to 536.0 ng/mL (mean 95.3 ng/mL) [to convert to ug/L, multiply by 1); majority of the patients (66%) had non-stage IV carcinoma; the commonest Gleason grade was 8 (33%); the mean survival of the total of 51 cases to be reported (42 previously reported cases and their 9 cases) was 29 months. Warner et al. [1] also stated that the diagnosis of primary signet ring cell carcinoma of the prostate was best confirmed by means of negative findings on gastrointestinal work-up, a positive stain for prostate-specific acid phosphatase, and negative carcinoembryonic antigen test results.

Selma et al. [9] reported a 76-year-old man with signet-ring-cell and adenocarcinoma of the prostate gland. They reported that the tumour was positively stained on immunohistochemistry for prostate-specific antigen and negatively stained for alcian blue and mucin.

Kastenbaum and Liman [10] reported a case of signet-ring carcinoma of the prostate gland in a patient who underwent prostatectomy. They reported that histological examination of the specimen had shown that the tumour was poorly differentiated signet-ring cell adenocarcinoma of the prostate Gleason 5+4 = 9 in 50% of the prostate with histological evidence of extra-prostatic extension as well as multifocal involvement of the surgical margins by invasive carcinoma. There was also lymphovascular and perineural invasion. The seminal vesicles were not involved. There was histological evidence of metastatic prostatic adenocarcinoma in 1 out of 3 pelvic lymph nodes. The tumour was staged as pT3N1MX. The authors did not report the long-term outcome. Kastenbaum and Liman [10] stated that:

- Besides the typical acinar histological pattern of adenocarcinoma of the prostate gland, several other histological patterns do exist including: atrophic, pseudo-hyperplastic, foamy gland, colloid and signet cell, oncocytic, lymphoepithelioma-like, and sarcomatoid (carcinosarcoma) variants. [11]
- Signet ring cell carcinoma of the prostate is rare and signet ring carcinomas with large cytoplasmic vacuoles displacing the nucleus should comprise at least 20% to 25% of the tumour [12] [13] [14] [15] [16] [17]
- In view of the fact that signet ring cell carcinomas (SRCCs) are known to occur in the breast, pancreas, stomach, colon, and urinary bladder and similar non-mucus secreting cells can be found in

lymphomas, thyroid tumours, oligodendrogliomas, and smooth muscle tumours alternative primary tumours must be excluded. These tumours tend to express prostate-specific antigen (PSA) and prostate specific acid phosphatase (PSAP), and may also express pancytokeratin but do not stain for carcinoembryonic antigen, cytokeratin 7, cytokeratin 20, synaptophysin, other lymphocytic or smooth muscle markers [15] [17]. The vacuoles might not contain mucin and as such may fail to stain on immunohistochemistry for mucicarmine, PAS, PASD, or Alcian Blue. Adjacent adenocarcinoma of the typical prostatic acinar type may be supportive of a diagnosis of primary signet ring cell adenocarcinoma of the prostate.

Fujita et al. [14] reported a 75-year-old man who was referred because his routine serum prostate-specific antigen (PSA) level was 9.3 ng / ml. His serum prostatic acid phosphatase (PAP) and carcinoembryonic acid (CEA) levels were normal. He had magnetic resonance imaging (MRI) scan which showed a low-intensity lesion in the right peripheral zone on T2-weighted images which was enhanced after intravenous contrast administration on T1-weighted images. He underwent trans-rectal ultrasound guided sextant biopsy of the prostate. Histological examination of the prostate biopsy specimens had shown that, 90% of all three specimens from the right lobe of the prostate consisted of signet-ring cells with large vacuolated cytoplasm displacing and compressing the nuclei. He underwent upper gastrointestinal endoscopy, barium enema, CT scan of abdomen, pelvis and thorax, chest X-ray, intravenous urography, bone scan and cystoscopy which did not reveal any malignancy in the gastro-intestinal tract or anywhere else. A diagnosis of primary signet-ring cell carcinoma of the prostate stage T2aNOM0 was made. He was given bicalutamide 80 mg per day and after one month his serum PSA level had dropped to 0.26 ng/ml and he underwent retro-pubic radical prostatectomy and pelvic lymph node dissection. Histological examination showed signet-ring cell carcinoma with poorly differentiated adenocarcinoma which was confined to the prostate with no evidence of lymph-node involvement. The signet-ring cell carcinoma consisted of about 30% of the tumour which showed degeneration as a result of the hormonal treatment the patient had had. Immunohistochemistry of the specimen showed positive staining with PSA, PAP, and keratin and negative staining for carcinoembryonic antigen (CEA), leucocyte common antigen (LCA), α-smooth muscle actin (α-SMA) and S100. Furthermore, the signet-ring cell carcinoma did not stain with periodic acid Schiff (PAS) with or without diastase pretreatment. The tumour also did not stain with Alcian blue. The patient was alive with no disease at 12 months pursuant to his operation and with his serum PSA level normal (less than 0.008 ng / ml). It would be argued that: this case report had illustrated the careful steps that are taken in the investigation and diagnosis of primary signet-ring cell carcinoma of the prostate and ensuring that a possible primary tumour elsewhere had been excluded; the patient was treated by a treatment option with curative intent; nevertheless, the case was reported at a time when long-term follow-up data was not available therefore whether or not the patient would survive for a long time cannot be told.

Vasiu et al. [18] reported a 71-years-old man who presented with non-specific lower urinary tract symptoms due to bladder outlet obstruction. He underwent trans-urethral resection of prostate and histological examination of all the 26 slides of the specimen showed signet ring cell adenocarcinoma of prostate with evidence of round to oval cells, vacuolated cytoplasm and peripherally located nucleus. The tumour cells were isolated and scattered the bundles of muscular and conjunctive cells. Some isolated prostatic glands were observed among the tumour cells and were normal in appearance and one of these glands was noted to have two signet ring cells on the wall. There was no evidence of lymphovascular or perineural involvement of the tumour. Immunohistochemistry was negative for PAS and mucicarmin. The paper was published at a time when there was no long-term follow-up data. Vasiu et al. [18] stated that there are many definitions for signet-ring cell carcinoma of the prostate but as a rule of thumb iterated by some people the diagnosis of signet-ring cell adenocarcinoma of prostate is assigned when there are present at least 25% of typical signet-ring cells in the tumour.

Celik et al, [19] in 2014 reported a 66-year-old man who was referred because of lower urinary tract symptoms. Digital rectal examination revealed a hard prostate. His serum PSA was 100 ng / dl. He had bone scan which showed evidence of bony metastases. He had trans-rectal ultrasound scan guided biopsies of the prostate in which 10 biopsies were taken. Histological examination of the prostate revealed Gleason 4 + 5 = 9 adenocarcinoma of prostate in all the ten biopsies. He had computed

tomography scan of abdomen and pelvis which showed bilateral hydronephrosis and enlarged para-aortic and para-iliac lymph nodes. He went into urinary retention and was catheterized. His serum PSA level had risen to 6658 ng / dl and his isotope bone scan had shown dense metastasis to the vertebra. He underwent trans-urethral resection of prostate and histological examination of the specimens showed poorly differentiated signet-ring cell adenocarcinoma of prostate Gleason 5 + 5 = 10. He had further investigations which excluded an extra-prostatic primary tumour. After he had received 3 months of hormonal treatment his serum PSA level had decreased to 441 ng / dl and following this his serum PSA level had increased again. He then received leuprolide acetate and anti-androgen therapy and after nine months his serum PSA level had decreased to 84.4 ng / dl and his serum testosterone level was < 20 ng / ml. Subsequently his serum PSA level had increased and 3 months later his serum PSA level was 271 ng / dl. He was adjudged to have castrate resistant prostate cancer and he was therefore put on Docetaxel which he received on day one of a 3-week cycle with a dose of 75 mg / m2 with a 3-week cycle. After he had received 12 cycles of treatment his symptoms had improved but his serum PSA level had remained between 200 and 281 ng / dl. He developed urosepsis whilst he was undergoing chemotherapy for which he was treated with antibiotics. Nevertheless, he died of urosepsis after 22 months. The authors explained that they had to use Docetaxel because of the rapid serum PSA doubling time and the castrate resistance state of the carcinoma in this case.

Mudholkar et al. [20] reported an 85-year-old man who presented with a 2 months history of dysuria, diurnal frequency, nocturia and he was clinically found to have been in retention of urine on presentation. On digital rectal examination he was found to have a stony hard prostate with a grade 3 enlargement. His serum PSA level was 33.7 ng / ml. He was catheterized. His haematological and biochemistry investigations were normal. He had needle biopsy of prostate and histological examination of the specimen revealed poorly differentiated adenocarcinoma of prostate. His chest X-ray and computed tomography scan of abdomen and pelvis did not reveal any metastasis. He underwent cystoscopy and trans-urethral resection of prostate which involved mainly the lateral lobes and multiple grey-white tissue of the prostate tissue, was resected. Histological examination of the specimen revealed classic signet-ring cell carcinoma showing round to oval cells, vacuolated cytoplasm and a peripherally located nucleus arranged in nests, sheets and isolated cell forms. Some isolated prostatic glands which had signet-ring morphology as well as normal looking prostatic gland were seen in the tumour. There was evidence of vascular invasion in the tumour. Immunohistochemistry of the tumour was positive for PSA. Special stain for mucin like PAS stain was done to exclude secondary signet ring cell adenocarcinoma arising from a primary tumour elsewhere metastasizing into the prostate this was negative for mucin. He had remained well with no evidence of metastasis at 6 months of follow-up. There was no long-term follow up data on the patient at the time of publication of the paper.

Khan et al. [21] reported a 74-year-old man who presented with a 3 month history of lower urinary tract symptoms including frequency and dysuria. His serum PSA was 9.71 ng/ml. He had trans-rectal ultrasound scan of prostate which showed an enlarged prostate and hypo-echoic areas in the peripheral zone of the prostate. Rectal examination revealed that the prostate gland was elastic, slightly hard, and painless. He had a chest X-ray which was normal. He underwent cystoscopy which did not reveal any pathology in the urinary bladder and this was followed by trans-urethral resection of prostate. Histological examination of the specimen showed nests and singly infiltrating poorly differentiated, hyperchromatic, pleomorphic adenocarcinoma cells, most of which were of signet ring morphology. Individual cells and cell nests were observed to be lying, hapharzardly among bundles of smooth muscle fibers and also within the lymphovascular spaces; nevertheless, there was no evidence of perineural invasion, mucinous fibroplasia, or glomerulations. Based upon these findings a provisional diagnosis of poorly differentiated signet-ring cell variant of adenocarcinoma of prostate Gleason 4 + 5 = 9 was considered. However, immunohistochemistry for PSA and carcinoembryonic acid (CEA) were negative. The globoid optically clear cytoplasm of the signet ring cells were stained positively with Alcian blue at PH 2.5 which confirmed the contents to be acid mucin. These findings inclusive of negative immunohistochemistry for PSA did illustrate that the prostatic signet ring carcinoma was not a primary tumour. Two weeks after the patient had undergone trans-urethral resection of prostate, he underwent upper gastrointestinal endoscopy and biopsy of a lesion in his stomach. Histological examination of the specimen showed presence of signet-ring cell carcinoma of the stomach. He had a computed tomography scan which showed enlarged regional

lymph nodes but no evidence of involvement of the liver or any other organ. He underwent radical gastrectomy and follow-up chemotherapy. At the time of the report of the case, 6 months after he had undergone trans-urethral resection of prostate the patient was alive and well. This case report has illustrated the careful way of assessing a patient with signet-ring cell carcinoma of the prostate gland in order to confirm whether or not the carcinoma is primary or metastatic and in this particular case it was a metastatic signet-ring cell carcinoma of prostate which had developed from a primary gastric signet-ring cell carcinoma. This case also shows that at times symptoms emanating from a metastatic tumour may be the first presenting symptoms which could eventually lead to the diagnosis of the primary tumour after thorough investigation.

Kwon et al. in 2008 [22] reported a 61-year-old man who was referred because of lower urinary tract symptoms of urinary diurnal frequency and nocturia of 4 months duration. He had a high serum prostate-specific antigen (PSA) level (8.1 mg / ml). He had trans-rectal ultrasound scan biopsy of prostate and histological examination of the specimen had shown benign prostatic tissue. Three years later, he was seen again because his serum PSA level had risen to 14.7 ng/ml and he also had back pain. He had another trans-rectal ultrasound scan guided biopsy of prostate. Histological examination and immunohistochemistry of the specimen showed signet-ring cell carcinoma of prostate. Signet-ring cell-like lesion was found suggestive of adenocarcinoma in 1 of the 12 pieces of biopsy in 20% of the tumour volume. Pathological examination of the specimen showed that the tumour cells had marked cytological and nuclear pleomorphism, admixed with spindle cells, histiocyte-like cells. Cellularity was noted to be high, and cellular atypia, nuclear pleomorphism, mitoses, abnormal mitoses and tumour necrosis were also seen. Immunohistochemical studies of the tumour had shown the following staining characteristics: Pan-cytokeratin (Pan-CK) was diffuse 2 positively stained; PSA was focal 3 positively stained; high molecular weight cytokeratin (HMW-CK) was negative; CD 68 staining was positive on scattered histiocytes; and P504S was focally 1 positive. He had computed tomography (CT) scan, magnetic resonance (MRI) scan, and isotope bone scan which showed multiple bone metastases. He had upper and lower gastrointestinal endoscopies which excluded any lesion in the colon, stomach and duodenum. With the knowledge that the results of the radiological investigations and the endoscopic procedures had excluded an extra-prostatic origin signet-ring cell carcinoma metastasizing to the prostate a diagnosis of primary signet-ring cell carcinoma of prostate (cT2N0M1b) was made. He was started on Androgen deprivation therapy (ADT). Nine months later, he was diagnosed as having hormone refractory prostate cancer (HRPC) and the androgen deprivation therapy was stopped and he was started on Docetaxel chemotherapy. The patient died after he had received 2 cycles of chemotherapy.

Dols et al. in 2005 [23] reported a 60-year-old man, who five years earlier, had undergone gastrectomy to resect signet-ring carcinoma of the stomach involving the gastric antrum. The tumour was stage T4N1M0 and the patient received 6 cycles of adjuvant combination chemotherapy which included epirubicin, cisplatin and 5-fluorouracil (ECF). He subsequently presented with voiding symptoms and he had a CT scan which showed pyelocalyceal dilatation I-II/IV. His serum PSA was 0.84 ng / ml. He had rectal examination which revealed an enlarged prostate with an irregular surface with micro-nodules on both lobes suggestive of malignancy. He had trans-rectal ultrasound scan of prostate which showed both the prostate and the seminal vesicle were involved by a lesion and histological examination of the biopsy specimens showed that the prostate and the seminal vesicles had been infiltrated with mucino-secretory adenocarcinoma with signet-ring cells of gastric origin. The histology of biopsies from the prostate was compared with that of the gastrectomy specimen. Immunohistochemistry of the prostate tumour biopsy specimen was negative for PSA and positive for cytokeratin 20 (CK 20). He had magnetic resonance imaging scan and PET scan which excluded tumour anywhere else in the body. Dols et al. [23] therefore, diagnosed a secondary intra-prostatic spread of the primary signet-ring cell carcinoma of the stomach when the patient had urinary tract obstruction. The patient was treated by means of radiotherapy between 22nd March 2004 and 10th May 2004. There was no report relating to long-term follow-up of this case because the case was reported early when there was no long-term follow-up. Dols et al. [23] stated that their case was the sixth reported case with a diagnosis of a secondary signet-ring cell tumour of the prostate secondary to a gastric cancer. They also stated that when clinicians are confronted with intra-prostatic signet-ring cell adenocarcinoma it would be necessary to distinguish between primary and secondary

aetiology in view of the fact that this would reflect in the choice of treatment and prognosis.

Kang et al. [24] reported two cases of primary signet-ring cell carcinoma of the prostate which had arisen in a 79-year-old man and a 65-year-old man. Both cases were poorly differentiated adenocarcinoma of the prostate gland with many signet-ring cells. Kang et al. [24] reported that on immunohistochemical staining the signet-ring cells were positive for prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) but they were negative for neural and acid mucins. Kang et al. [24] stated that at the time of their report in 1999, about 18 cases had been reported in the literature. Kang et al. [24] summarized that: Signet-ring cell adenocarcinoma of the prostate gland is a rare variant of poorly differentiated adenocarcinoma of the prostate gland. The origin of the prostate should be considered in cases of metastatic signet-ring cell carcinoma, particularly when the signet-ring cells are negative for neutral and acid mucins. Tests for prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) should also be performed to confirm the primary signet-ring cell carcinoma of prostate.

Ro et al. in 1988 [25] reported eight patients with adenocarcinomas of the prostate gland containing significant numbers of signet-ring cells, one of the patients had presented initially with supra-clavicular lymph node metastasis. Ro et al. [25] reported that the ages of the patients had ranged from 50 years to 80 years and the mean age of the patients was 67.5 years. None of the patients had received any form of treatment before biopsy or surgery. All of the patients were found at presentation to have advanced disease (five with stage C carcinoma and three with stage D carcinoma). All the tumours were poorly differentiated adenocarcinomas, M D Anderson Hospital system grade IV, Gleason's combined scores of 9 or 10. The signet-ring cells were negative for neutral and acid mucins but immunoreactive for prostate specific-antigen (PSA) and prostatic-specific acid phosphatase (PAP). With regard to the ultrastructural appearances of the tumours, the signet-ring cell appearance resulted either from the presence of intra-cytoplasmic lumina or from vacuoles. Signet-ring cells were also present at metastatic sites. Ro et al. [25] concluded that: (a) Signet-ring cell carcinoma of the prostate is a variant of poorly differentiated adenocarcinoma of the prostate gland and (b) when a metastatic signet-ring–cell carcinoma with intracytoplasmic mucin is identified, origin from the prostate gland should be considered, and immunohistochemistry for prostate-specific antigen (PSA) and prostatic-specific acid phosphatase (PAP) should be performed.

Hashimoto et al. [26] in 2008 reported a 61-year-old Japanese man who was found to have left cervical lymph adenopathy. He had left cervical lymph node biopsy and histological examination of the specimen was reported as having shown metastatic signet-ring cell carcinoma. He had positron emission tomography CT (PET CT) scan and fluorodeoxyglucose (FDG) uptake was detected in the left side of the neck, right lobe of the liver, the fifth to 7^{th} cervical vertebrae, the right ischium, the pelvic lymph nodes, and lesions in the prostate gland (see figure 1). Even though FDG uptake was observed in the thyroid gland, it was diagnosed as chronic thyroiditis following close inspection. The gastrointestinal examination was normal. He had rectal examination which revealed an enlarged stony hard prostate. The serum PSA level was 0.19 ng / ml. He underwent urethrocystoscopy which revealed a normal prostatic urethra and urinary bladder. He underwent trans-rectal ultrasound guided biopsies of prostate in which 10 biopsies were taken. Histological examination showed signet-ring cell carcinoma in all the specimens (see figure 2) Immunohistochemical staining of all the carcinoma cells stained negatively for PSA. Despite extensive general examinations there was no evidence of primary carcinoma anywhere else. As a result despite the immunohistochemistry finding for PSA and normal serum PSA a final diagnosis of signet-ring-cell carcinoma of prostate with a clinical stage of T3N2M2 was made. He received combination chemotherapy which consisted of estramustine, docetaxel, and carboplatin chemotherapy. After he had received 2 courses of the combination chemotherapy he had another PET CT scan which had shown reductions in the size of the prostate gland as well as reduction in the FDG uptake in the prostate and sites of metastasis (see figure 3). He received another 2 courses of the same combination chemotherapy; nevertheless, his liver metastasis progressed. In view of the progress of the liver metastasis despite being on 1^{st} line combination chemotherapy, he then received a 2^{nd} line combination chemotherapy which consisted of TS-1 and CPT-II. He received 2 courses of this second line chemotherapy but his disease progressed and he died of disseminated metastatic disease 16 months pursuant to his initial presentation. Hashimoto et al. [26] stated the following:

- About 100 cases of signet-ring-cell carcinomas of the prostate have been reported. [1]
- Some authors [27] [28] had iterated that diagnosis of signet-ring cell carcinoma requires that 25% or more of the tumour should be composed of signet-ring cells.
- Clinically signet-ring cell carcinoma is most commonly diagnosed in an advanced stage of disease through elevated serum PSA levels. Nevertheless, some cases of signet-ring-cell carcinomas have high carcinoembryonic antigen (CEA) immunoreactivity whilst PSA is negative. [29]
- Some authors had indicated that PSA may be absent, particularly in cases of poorly differentiated carcinomas of the prostate. Yamamoto et al. [30] had reported 8 patients who had clinically metastatic carcinoma of the prostate gland, and their serum PSAs were less than 10 ng/ml. Most of the patients had poorly differentiated or undifferentiated tumours which were associated with poor prognosis in comparison with the usual metastatic carcinoma of the prostate gland. Yamamoto et al. [30] also noted that androgen deprivation therapy was not effective in these cases and in view of this they would recommend systemic chemotherapy and radiotherapy.

The lesson learnt from this paper would indicate that perhaps the chemotherapeutic regimens available as 1st line and 2nd line therapy may not be very effective in the treatment of some or all signet-ring-cell carcinomas and that there is the need to find or develop other chemotherapy drugs that are capable of improving the outcome of signet ring cell carcinomas of prostate.

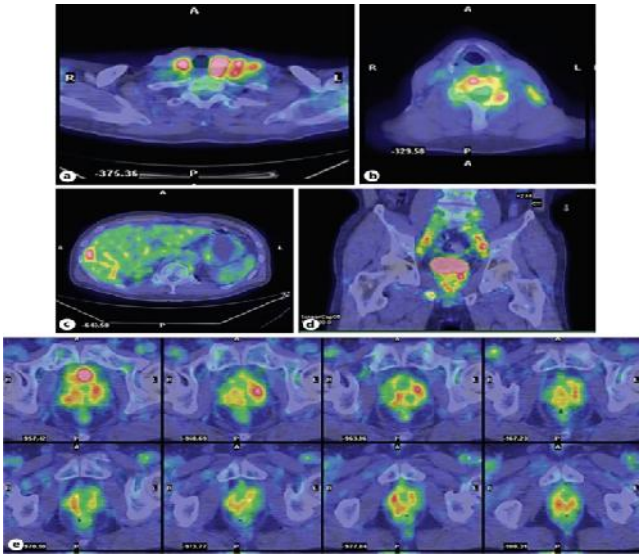

Figure 1: PET CT showed FDG uptake in the left neck (a), C5 – 7 (b), right lobe of liver (c), right ischium, pelvic lymph node, (d), and prostate (e) Reproduced from [26] Hashimoto Y, Imanishi K, Okamoto A, Sasaki A, Saitoh H, Wada R, Yamamoto H, Koie T, Onyama C. An Aggressive Signet Ring Cell Carcinoma of the Prostate in a Japanese Man. Case Rep. Oncol 2011 Sep – Dec; 4(3): 517 – 520. Doi: 10.1159/000334081 Copyright © 2011 by S Karger AG, Basel. This is an Open Access article distributed under the terms of the Creative Commons Attribution-Noncommercial-No-Derivative-Works License (http://creativecommons.org/licenses/by-nc-nd/3.0). Users may download, print and share this work on the internet for noncommercial purposes only, provided the original work is properly cited, and a link to the work on htpp://www.karger.com and the terms of this license are included in any shared versions.

Torbenson et al. [31] in 1998, had stated that adenocarcinoma of the prostate with a signet ring cell (SRC) component was rare, incompletely characterized variant of carcinoma of the prostate which must be distinguished from similar tumours of the urinary bladder and gastric origin. They stated that in their study, they had used mucin, and immunoperoxidase stains on formalin-fixed, paraffin-embedded sections from 12 adenocarcinomas of the prostate gland with signet-ring cell components, with antibodies to prostate-specific antigen (PSA), cytokeratins, MIB-1, bcl-2, c-MET, CD44v6, and CD44v7. They had performed a comparison study on six urinary bladder and seven gastric carcinomas with signet-ring cells. They found that the prostatic signet-ring cell component was always associated with the usual high-grade adenocarcinoma. Both components were positive for PSA, AE1/AE3, and CAM 5.2 in 12 cases out of 12; Five cases out of 9 had expressed c-MET; Nine out of 10 cases had expressed CD44v6; Nine out of 10 cases had expressed CDv7; only rare cells stained for bcl-2 (3 cases out of 9); the mean MIB-1 proliferation index was 8%. They had also identified the following: Intracellular mucin (periodic acid-Schiff with diastase pre-digestion (PAS-D) in 9 cases out of 10; mucicarmine in 5 out of 10 cases; alcian blue in 6 out of 10 cases. They also reported that the urinary bladder and gastric tumours were positive for PSA in 3 cases out of 6 and in 2 cases out of 7, respectively using a polyclonal antibody; for bcl-2 5 cases out of 6 and 2 cases out of 7 were positive respectively for the urinary bladder and gastric carcinomas; for c-MET, 6 out of 6 of the urinary bladder carcinomas and 6 out of 7 gastric carcinomas were positive; for CD44v6, 5 out of 6 of the urinary bladder carcinomas were positive and 6 out of 7 gastric carcinomas were positive; for CD44v7, 4 out of 6 urinary bladder carcinomas were

positive and 4 out of 7 gastric carcinomas were positive; the mean MIB-1proliferation indices were 15% for the urinary bladder carcinomas and 35% for the gastric carcinomas; all the tumours were negative for cytokeratin 34β E12.

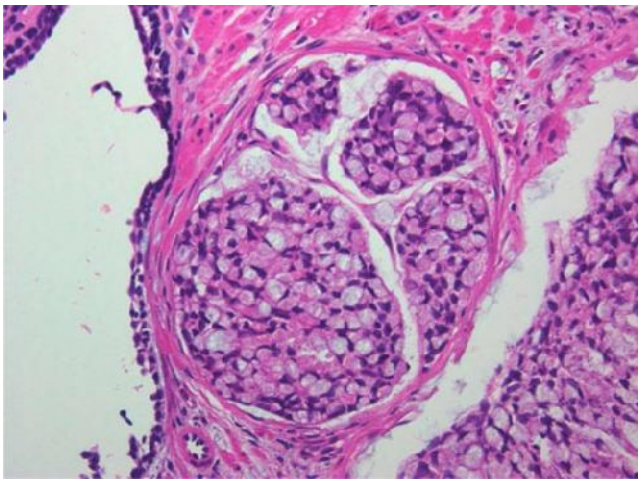

Figure 2: The microscopic findings of prostatic specimens. More than 50% of atypical cells were signet ring cells (HE stain, original magnification x 200)

Reproduced from [26] Hashimoto Y, Imanishi K, Okamoto A, Sasaki A, Saitoh H, Wada R, Yamamoto H, Koie T, Onyama C. An Aggressive Signet Ring Cell Carcinoma of the Prostate in a Japanese Man. Case Rep. Oncol 2011 Sep – Dec; 4(3): 517 – 520. Doi: 10.1159/000334081 Copyright © 2011 by S Karger AG, Basel. This is an Open Access article distributed under the terms of the Creative Commons Attribution-Noncommercial-No-Derivative-Works License (http://creativecommons.org/licenses/by-nc-nd/3.0). Users may download, print and share this work on the internet for noncommercial purposes only, provided the original work is properly cited, and a link to the work on htpp://www.karger.com and the terms of this license are included in any shared versions.

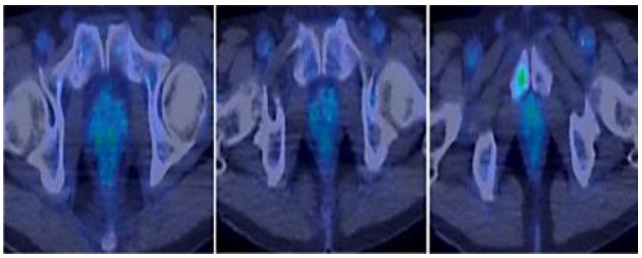

Figure 3: The image of PET- CT after 2 courses of estramustine, docetaxel, carboplatin combined chemotherapy. After chemotherapy, FDG uptake and prostatic volume were extremely reduced. Reproduced from [26] Hashimoto Y, Imanishi K, Okamoto A, Sasaki A, Saitoh H, Wada R, Yamamoto H, Koie T, Onyama C. An Aggressive Signet Ring Cell Carcinoma of the Prostate in a Japanese Man. Case Rep. Oncol 2011 Sep – Dec; 4(3): 517 – 520. Doi: 10.1159/000334081 Copyright © 2011 by S Karger AG, Basel. This is an Open Access article distributed under the terms of the Creative Commons Attribution-Noncommercial-No-Derivative-Works License (http://creativecommons.org/licenses/by-nc-nd/3.0). Users may download, print and share this work on the internet for noncommercial purposes only, provided the original work is properly cited, and a link to the work on htpp://www.karger.com and the terms of this license are included in any shared versions.

Torbenson et al. [31] concluded that adenocarcinomas of the prostate gland with signet-ring cell components:

- Are typically accompanied by high-grade adenocarcinomas.
- Are variably positive for mucin, with PAS-D being the most sensitive stain.
- Show expression of PSA, cytokeratins, MIB-1, bcl-2, c-MET, and CD44 similar to that shown by high-grade adenocarcinoma components.
- Have a low MIB-1 proliferation index.
- Are not always distinguishable from signet-ring cell components of urinary bladder and stomach carcinomas with any of the above stains, including PSA.

Wang et al. [8] examined the epidemiology, natural history, treatment pattern, and predictors of long-term survival of signet-ring cell carcinoma patients based upon the analysis of the national Surveillance, Epidemiology, and End Results (SEER) data base. Wang et al. [8] reported that they had identified a total of 93 patients who between 1980 and 2004 had pathologically confirmed signet-ring-cell carcinoma of prostate. The mean age of the patients was 70 ± 11 years old. 82.8% of the patients were diagnosed as having poorly differentiated or undifferentiated histological grade tumours. 13.9% of the patients were found to have had metastatic disease at the time of their presentation. The 1-year, 3-year, and 5-year cancer-specific survival rates were 94.6%, 89.6%, and 83.8% respectively. They had found out from using multivariate Cox proportional harzard model, that younger age (40 – 50 years versus age > 70 years, P = .01), advanced tumour stage (distant versus local /regional, P=.02), and earlier diagnosis year (before 1995 versus after 1995, P=.01) were predictors of worse cancer-specific survival. Wang et al. [8] concluded that: Despite more aggressive cancer therapy younger patients who

were afflicted by signet-ring-cell carcinoma of the prostate gland had a worse cancer specific survival; this information could be useful when these patients are being counselled and emphasizes the need for new strategies and molecular-based therapeutic approaches for younger patients with primary signet-ring-cell carcinoma of the prostate gland.

Conclusions

Primary SRCCPs tend to be high-grade/undifferentiated tumours with poor prognosis but recent data though anecdotal had stated improvement in prognosis, the prognosis for the younger age group remains poor. New cases of primary SRCCP should be entered into a multi-center trial to decide on the best treatment options and to find out if the prognosis would be influenced by the percentage of signet-ring cells. There is need to have a consensus opinion on the minimum proportion of signet-ring cells in a prostatic tumour that would constitute primary SRCCP.

Conflict of interest: None

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