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Signet-Ring Cell adenocarcinoma of the Urinary Bladder: A Review of the Literature

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Abstract

Signet-ring cell carcinoma of the urinary bladder is a rare tumour which most clinicians have not encountered in their practice. We have reviewed the literature on signet-ring cell carcinoma of the urinary bladder in order to document its presentation, diagnosis, differential diagnosis, management and management outcome. Various internet search engines were used to identify case reports, case series and review papers on signet-ring cell carcinoma which formed the pivot for the literature review. Signet-ring cell adeno carcinoma of the urinary bladder is a relatively rare variant of adenocarcinoma of the urinary bladder. It has signet-ring type cells with intracytoplasmic mucin. This diagnosis is limited to 25% or more signet-ring type cells in the bladder tumour. Signet-ring cell adenocarcinomas of the urinary bladder occur more commonly in females and they tend to present with haematuria. Signet-ring cell adenocarcinoma exhibits diffuse infiltration of the bladder similar to that of linitis plastica of the stomach and it is associated with poor prognosis. Histological examination of the bladder characteristically shows signet-ring type cells which on immunohistochemical staining stain positively with cytoleratin and usually with mucin. Signet-ring cell adenocarcinoma of the urinary bladder may be primary or it may be secondary from stomach, breast or from other organs or direct extension from the prostate or rectal adenocarcinoma. Cystectomy is the treatment of choice that would improve the prognosis of primary signet-ring cell adenocarcinoma of the urinary bladder. Signet-ring cell adenocarcinoma of the urinary bladder is a relatively rare tumour which could be: (a) a primary tumour; (b) result of direct extension from adenocarcinoma of prostate or rectum; (c) a metastatic tumour with the primary tumour originating from elsewhere including the stomach and breast. When a signet-ring cell carcinoma of the bladder is found on histological examination the patient should be carefully investigated to exclude metastatic tumour or direct extension from nearby organs. In cases of primary signet-ring cell carcinoma of the urinary bladder so far cystectomy is the treatment that would improve survival.

Key Words: Signet-ring cell carcinoma; urinary bladder; Gross appearance; Macroscopic; Microscopic; Immunohistochemistry, Cytokeratin, Mucin

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Introduction

Haematuria is a commonly encountered symptom in urological practice. Haematuria quite often represents the presence of serious disease such as malignancy in the urinary tract (carcinoma of urinary bladder, carcinoma of ureter, carcinoma of renal pelvis, carcinoma of the kidney). The majority of carcinomas of the urinary bladder tend to be primary carcinomas, and histologically these tumours usually are transitional cell carcinomas. This paper contains a review of the literature on signet-ring cell carcinoma of the urinary bladder (primary and metastatic).

Literature Review

Definition: Signet-ring cell adenocarcinoma of the urinary bladder is an uncommon tumour with signet-ring type cells with intracytoplasmic mucin involving the urinary bladder. It has been recommended that signet-ring cell adenocarcinoma should be limited to cases with 25% or more signet-ring tumour cells [1]

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Epidemiology

Grignon et al. [2] stated that primary signet-ring cell carcinoma of the urinary bladder occurs more commonly in men than in women and with a median age of 58 years.

Presentation

Grignon et al. [2] stated that the most frequent presentation of primary signet-ring cell carcinoma of the urinary bladder is haematuria.

Clinical Features

Pernick [1] stated that signet-ring cell carcinoma of the urinary bladder exhibits diffuse infiltration which is similar to linitis plastica of the stomach and this makes resection of the tumour with curative intent virtually impossible (see details in discussion reference 1). Wang et al [3] stated that signet-ring cell carcinoma of the urinary bladder is very aggressive with poorer survival. However, presence of a few signet-ring cells does not affect the prognosis of a bladder adenocarcinoma.

Treatment

It has been stated that cystectomy in the treatment of signet-ring cell carcinoma of the urinary bladder may be important for improved survival. [1] [4]

Gross description

It has been stated that signet-ring cell carcinoma of the urinary bladder is usually non-urachal; Signet-ring cell carcinoma of the urinary bladder may lack mucosal involvement; Signet-ring cell carcinoma of the urinary bladder is diffusely infiltrative. [1]

Microscopic characteristics

Pernick [1] summarized the microscopic characteristics of signet-ring cell carcinoma of the urinary bladder as follows:

- Urinary bladder tumour exhibits signet-ring type cells with intracytoplasmic mucin, which resemble lobular carcinoma of breast but they tend to be larger.
- Signet-ring cell carcinoma of the urinary bladder may have monocytoid cells with central nuclei.
- Urothelial abnormalities may be difficult to find in signet-ring cell carcinoma of the urinary bladder.
- No abundant extracellular mucin can be found in signet-ring cell carcinoma of the urinary bladder.

(See figure 1 which shows urothelial mucosa and underlying adenocarcinoma in a urinary bladder; figures 2, 3 and 4 which show signet-ring cell adenocarcinoma of urinary bladder of a patient who had signet-ring cell carcinoma of the urinary bladder)

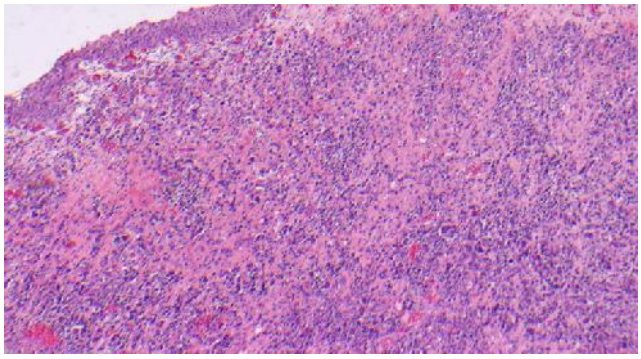

Figure 1: Signet ring cell carcinoma of urinary bladder Haematoxylin and Eosin stain x 4 magnification. Urothelial mucosa on the surface and underlying adenocarcinoma.

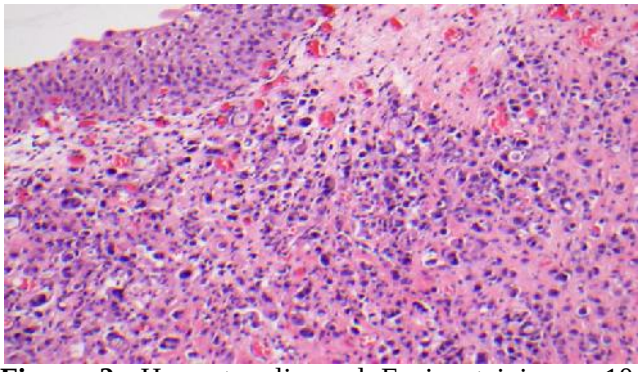

Figure 2: Haematoxylin and Eosin staining x 10 magnification showing signet-ring cell adenocarcinoma

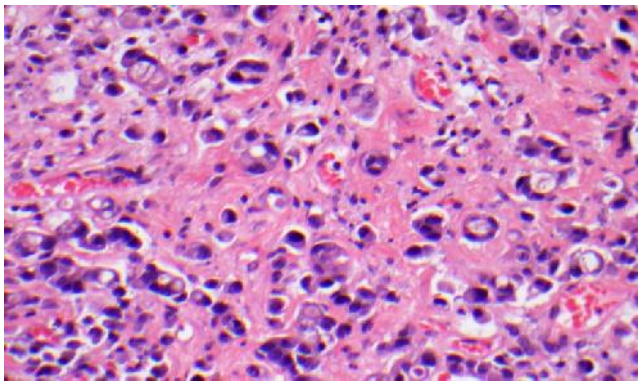

Figure 3: Haematoxylin and Eosin staining x 20 magnification showing signet-ring cell adenocarcinoma of the bladder

Immunohistochemical staining characteristics

Pernick [1] stated that signet-ring cell carcinoma of the urinary bladder stains positively with cytokeratin, and it usually stains with mucin, but it may not be prominent.

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(See figures 5, 6, and 7 which show positive immunohistochemical staining for CK7, CK19, and CK20 respectively and figures 8 and 9 which show negative immunohistochemical staining with urothelial markers GATA-3 and Uroplakin in the same patient who had signet-ring cell carcinoma tumor of the urinary bladder)

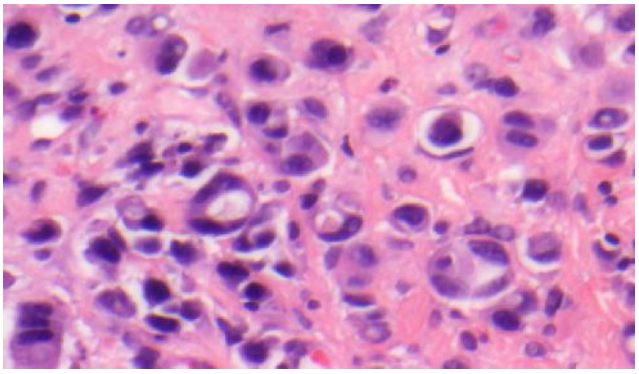

Figure 4: Haematoxylin and Eosin staining x 40 magnification showing signet-ring cell adenocarcinoma of urinary bladder (same tumour in 2 and 3 at higher magnification)

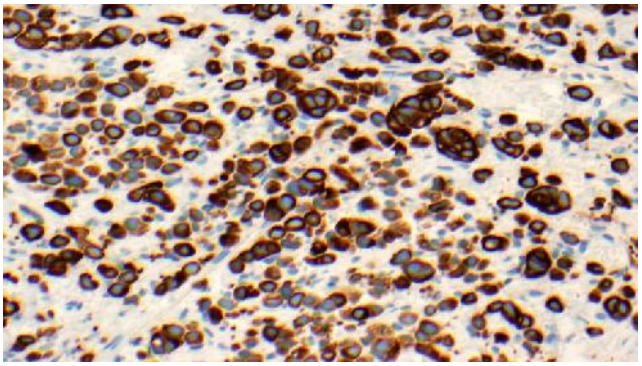

Figure 5: Immunohistochemical staining showing positive staining for CK7

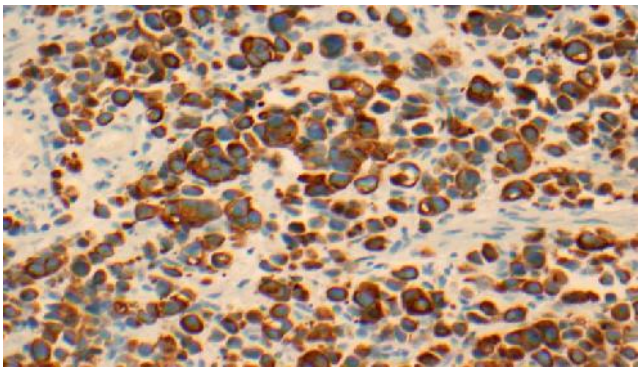

Figure 6: Immunohistochemical staining showing positive staining with CK19

Differential diagnosis

Pernick [1] stated that the differential diagnoses of signet-ring cell carcinoma of the urinary bladder include the following:

- Direct extension from carcinoma of the prostate gland or adenocarcinoma of the rectum.
- Metastases from stomach, breast, or other organs.
- Nodular histiocytic hyperplasia, which is rare was reported in lamina propria of the urinary bladder, and this may have mild atypia and mitoses, strong immunohistochemical staining with CD68+, keratin. [5]

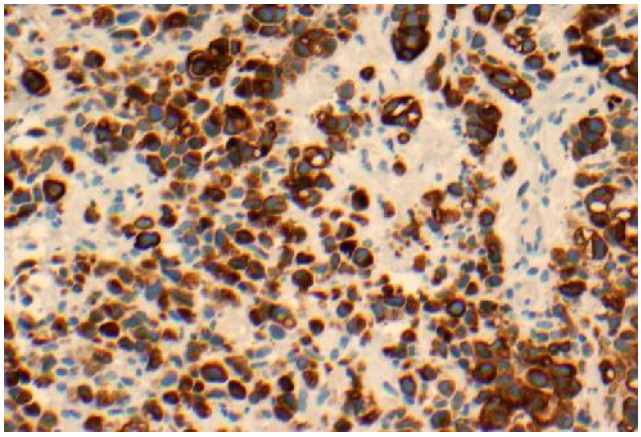

Figure 7: Immunohistochemical staining showing positive staining with CK20

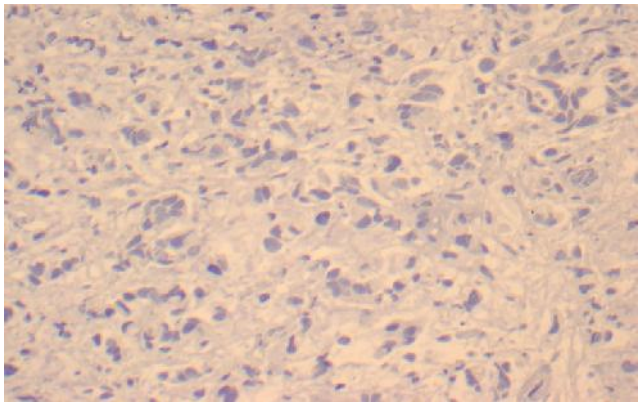

Figure 8: Immunohistochemical staining showing negative staining for urothelial marker GATA-3

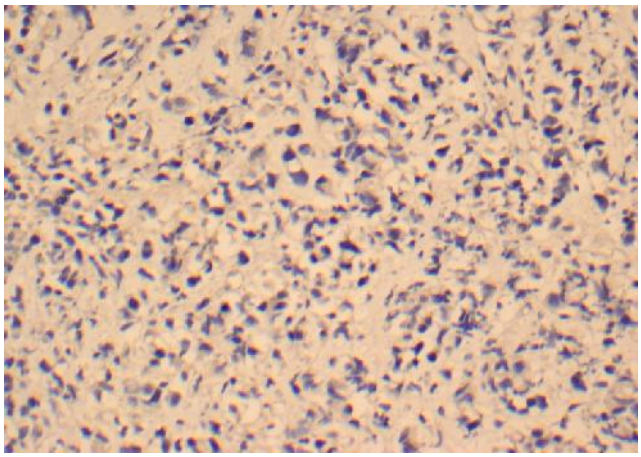

Figure 9: Immunohistochemical staining showing negative staining for urothelial marker Uroplakin

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Discussion

Pernick in 2011 [1] stated that signet-ring cell adenocarcinoma is an uncommon tumour which has signet ring cells with intracytoplasmic mucin. Pernick [1] recommended that the definition of signet-ring cell carcinoma should be limited to tumours with 25% or more signet-ring tumour cells. [1]

With regard to clinical features, Pernick [1] stated that signet-ring cell adenocarcinomas of the urinary bladder exhibit diffuse infiltration which is similar to linitis plastic of the stomach and this characteristic feature makes curative resection of the tumour virtually impossible. [1]

Pernick [1] stated that:

- Macroscopic examination of signet-ring cell adenocarcinomas of the urinary bladder reveal that the tumour (a) is usually non urachal, (b) may lack mucosal involvement, (c) is diffusely infiltrative.
- Microscopic examination of signet-ring cell adenocarcinoma of the urinary bladder (a) depicts signet-ring type cells with intracytoplasmic mucin which resembles lobular carcinoma of breast but the cells are larger, (b) may depict monocytoid cells with central nuclei, (c). In addition, urothelial abnormalities may be difficult to find in the microscopic examination as well as no abundant extracellular mucin may be seen.
- With regard to mmunohistochemical staining, signet-ring cell adenocarcinomas of the urinary bladder are positively stained for Cytokeratin and they are usually positively stained for mucin but this positivity may not be prominent.
- The differential diagnoses of primary signet-ring cell carcinoma of the urinary bladder include direct extension from prostatic or rectal adenocarcinoma; metastasis from stomach, breast or other organs

Grignon and associates [2] stated that in view of the fact that primary signet-ring cell carcinoma is an aggressive tumour most patients (up to 65%) tend to present with locally-advanced disease.

Wang and associates [3] used a population-based data set to compare the cancer specific survival of patients with signet-ring cell carcinoma versus transitional cell carcinoma of the urinary bladder. They identified signet-ring cell carcinomas of the urinary bladder and transitional cell carcinomas of the urinary bladder in the Surveillance, Epidemiology and End Results program (2001 to 2004). They compared the following: (a) demographic and pathological characteristics at diagnosis, (b) differences in cancer specific survival with univariate and multivariate Cox regression analysis. Wang and associates [3] reported their results as follows: A total of 103 signet-ring cell carcinomas of the urinary bladder were found in the database from 2001 to 2004. During that time 14,648 cases of transitional cell carcinoma of the urinary were diagnosed. Signet-ring cell carcinoma of the urinary bladder (a) was more common in younger patients than in older patients ($p<0.001$); (b) more commonly presented with high grade histology ($p<0.001$) and advanced stage disease ($p<0.001$). Wang and associates [3] additionally reported that:

- The 3-year cancer specific survival rate was 67.0% and 33.2% for transitional cell carcinoma of the urinary bladder and signet-ring cell carcinoma of the urinary bladder respectively.
- On multivariate analysis there was an increased mortality risk in patients with signet-ring cell carcinoma in comparison with transitional cell carcinoma (HR 1.42. 95% CI 1.03-1.97, $p<0.001$). When only high grade cases of signet-ring cell carcinomas of the urinary bladder and transitional cell carcinomas of the urinary bladder were compared, the result was still worse in signet-ring cell carcinoma (HR 1.430, 95% CI 1.035-1.976, 0.03). When only local stage of signet-ring cell carcinoma and transitional cell carcinoma were compared, the risk was worse in signet-ring cell carcinoma (HR 4.294, 95% CI 1.035-17.825, 0.045). Limited to patients who underwent cystectomy only, the difference in the cancer specific survival disappeared (HR 1.289, 95% CI 0.771-2.155, 0.33).

Wang and associates [3] concluded that even after adjusting for demographic, pathological and treatment factors, cancer specific survival is significantly worse in patients with signet-ring cell carcinoma of the urinary bladder than transitional cell carcinoma of the urinary bladder. They recommended that further research into the biology of this rare signet-ring cell carcinoma of the urinary bladder is required to explain these results.

Wang and Wang [4] examined the epidemiology, natural history, treatment pattern and predictors of long-term survival of patients with

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signet-ring cell carcinoma of the urinary bladder based upon the analysis of the national Surveillance, Epidemiology, and End Results (SEER) data base. Wang and Wang [4} reported that:

- In total 230 patients with pathologically confirmed signet-ring cell carcinoma of the urinary bladder, were identified between 1973 and 2004.
- The mean age was 65 ± 13 years.
- Overall, 75.7% of the patients had a poorly differentiated or undifferentiated histology grade, 26.5% presented with metastatic disease, 59 (25.7%) underwent trans-urethral resection for bladder tumour only and 107 (46.5%) had partial or radical cystectomy. The 1-, 3-, and 10-year cancer-specific survival rates were 66.8, 40.6, and 25.8%, respectively.
- Using multivariate Cox proportional hazard model, age (HR 1.024; $p = 0.004$), stage (distant versus local, HR 6.2; $p < 0.001$) and cystectomy (HR 0.53; $p = 0.002$) were identified as independent predictors for cancer-specific survival.

Wang and Wang [4] concluded that receipt of cystectomy was strongly associated with improved survival in the patients with signet-ring cell carcinoma of the urinary bladder. However, many patients with localized tumours did not receive potentially curative cystectomy. Wang and Wang [4**]** iterated that further studies to address the barriers to the delivery of appropriate care to these patients are warranted.

Ordonez et al et al. [5] reported four cases of histiocytic proliferation, two which occurred in the pleura in a 23-year-old woman and a 78-year-old woman, respectively, one in a hernia sac of a 2-year-old boy, and one in the lamina propria of the urinary bladder of a 74-year-old man with a non-invasive papillary transitional cell carcinoma. They stated that the morphologic features of the pleural lesion of the 23-year-old woman and of the hernia sac lesion of the 2-year-old boy, as well as the bladder lesion were similar to those reported in cases of the so-called mesothelial hyperplasia. The pleural lesion of the 78-year-old woman consisted of a proliferation of cells with a signet-ring-like morphology which was originally interpreted as either an unusual form of mesothelial hyperplasia or a metastatic signet-ring cell adenocarcinoma. Because of mitotic activity and some cellular atypia in the bladder lesion, the possibility of invasive transitional cell carcinoma into the lamina propria was considered before immunohistochemical stains were performed. Ordonez et al. [5] stated that immunohistochemical staining for keratin showed only a few positive cells in the hernia sac and pleural lesions, whereas most cells reacted for the histiocytic marker CD68. Immunohistochemical studies on the urinary bladder lesion also exhibited strong staining for CD68, but no reactivity for keratin was observed. Based upon the aforementioned results, Ordonez et al [5] concluded that all of the lesions were primarily reactive histiocytic proliferans and because they may occur in other locations aside from serosal membranes, the designation "nodular histiocytic hyperplasia" appeared to be more appropriate than nodular mesothelial hyperplasia. Ordonez et al [5] stated that it was important that the reactive nature of these lesions should be recognized because occasionally they may present high mitotic activity or may show signet-ring-like morphology and thus they can be confused with a malignancy.

Sandler and associates [6] stated that:

(a) Oesophageal carcinoma occurs in 3% of the population in the United Kingdom. However, in China and Iran the incidence of oesophageal carcinoma exceeds 100 per 100,000 individuals.
(b) In America, the incidence of oesophageal carcinoma is less than 5 per 100,000, even though the incidence rates are about quadruple for African Americans.
(c) The commonest site of oesophageal carcinoma is the lower third of the oesophagus, which is followed by the upper and middle third of the oesophagus.
(d) The Scottish Audit of Gastric and Oesophageal cancer discovered that adenocarcinoma of the oesophagus was more frequently found in comparison with squamous cell carcinoma in a ratio of 5:4.
(e) Oesophageal carcinoma is more common over the age of 55 years (with a median age of 72 years)
(f) Risk factors for the development of squamous cell carcinoma of the oesophagus include male sex, smoking, and alcohol and Barrett's oesophagus predisposes to adenocarcinoma of oesophagus.

Metastatic carcinoma to the urinary bladder from non-contiguous sites is extremely rare. Reports by some authors **[**7] [8] [9] indicate that between 2% and 12% of all tumours of the urinary bladder are secondary neoplasms.

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Ganem and associates [10] iterated that gross haematuria occurs relatively infrequently in secondary tumours of the urinary bladder in view of the fact that most lesions are small and infiltrate the urinary bladder wall without causing ulceration of the mucosa. Hence most metastases to the urinary bladder remain asymptomatic and quite often undiagnosed. [11]

Bates and associates [9] iterated that the urinary bladder can potentially be the recipient of metastatic tumour spread from a large variety of primary sites and most commonly direct invasion of tumour can occur from nearby/adjacent tumours of the lower gastrointestinal tract (13% of secondary neoplasms); prostate (19%); female genital tract 11%. Other authors have reported metastases to the urinary bladder from other less common primary sites including the stomach, skin, breast, and lung in descending frequency [10] [12] [13] [14].

Hargunani and associates [11] intimated that the management and prognosis of metastatic tumours to the urinary bladder differ significantly from that of primary urinary bladder tumours in view of the fact that they are frequently indicative of late disease.

Hargurani and associates [11] reported a 45-year-old male who presented with acute onset of visible haematuria. He had been diagnosed with adenocarcinoma of the distal oesophagus 2 years prior to his presentation with haematuria and he had undergone curative oesophageal tumour resection after he had completed neo-adjuvant chemotherapy. At the time of his oesophageal tumour resection, histological examination of the oesophageal tumour was consistent with poorly differentiated carcinoma with evidence of local lymph node spread. He had been regularly reviewed by the oncologists and he had remained asymptomatic until the onset of his visible haematuria.

He subsequently underwent cystoscopy which revealed a solid tumour in the urinary bladder on the right lateral wall and the tumour was treated by means of trans-urethral resection. Histological examination of the tumour depicted a poorly differentiated mucus-secreting adenocarcinoma, which was identical to the oesophageal tumour (The Haematoxylin and Eosin stained specimens of the original oesophageal adenocarcinoma and of the metastatic bladder tumour had the same histopathological features on microscopic examination). A diagnosis of metastatic oesophageal adenocarcinoma was made. A computed tomography scan did not demonstrate any pelvic tumour outside the urinary bladder and hence metastasis by the trans-coelomic route was essentially excluded, indicative of haematogenous spread of the primary oesophageal carcinoma. The patient was referred for further oncological therapy but unfortunately died 4 months later as a result of disseminated carcinoma. Hargunani and associates [11] stated that oesophageal cancer has the capability of spreading to all three neighbouring compartments (abdomen, chest and neck) and therefore has the potential of spreading to unusual sites. Hargurani and associates [11] stipulated that clinicians should always carefully regard haematuria in a patient who had previously undergone treatment for cancer and they should retain a high index of suspicion for distant metastases as being the cause.

Clark and associates [15] reported a 61-year-old-man who presented with dysphagia and weight loss. He underwent oesophagogastroscopy which revealed a lesion in the distal oesophagus which was biopsied. Histological examination of the specimen had depicted features of an adenocarcinoma arising from an area of Barrett's oesophagus. He had staging computed tomography scan and underwent laparoscopy which showed no evidence of metastatic disease. He then underwent oesophagogastrectomy from which he made an excellent recovery. The pathological stage of the tumour was pT3 N1 with the histology confirming a poorly differentiated adenocarcinoma involving 5 of 11 lymph nodes. The patient also received adjuvant radiotherapy with 50 Gy delivered in 20 fractions. He remained well and had a follow-up computed tomography scan 6 months pursuant to his surgical operation which showed small lung metastases and lytic deposits in thoracic vertebra 12. In view of this he received palliative radiotherapy to the latter area with good effect. One month later he presented to the Urology department with marked visible haematuria. He had upper renal tract imaging which was un-remarkable and he had a flexible cystoscopy which revealed a well circumscribed raised area at the dome of the urinary bladder which was not considered to be typical of transitional cell carcinoma. The provisional diagnosis at the time was either a primary adenocarcinoma of the urinary bladder possibly of urachal origin or metastatic disease. Trans-urethral resection of the tumour was performed. Histological examination of the tumour confirmed a poorly differentiated adenocarcinoma which was morphologically very similar to the primary oesophageal lesion. Immunohistochemical staining of the tumour was

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positive for CK7 and negative for CK20, PRAP again in keeping with metastatic disease. After a further episode of haematuria bladder wash outs and further cystodiathermy was required prior to palliative radiotherapy which was given to the urinary bladder with good effect and no further bleeding was reported. His further treatment plan included symptom control with input from the palliative care team. The report did not include long-term follow-up outcome.

Schuurman and associates [16] reported a solitary macroscopic metastasis of an adenocarcinoma of the oesophagus which was located in the urinary bladder and which had similar histological characteristics of the oesophageal carcinoma. Immuno-histochemical staining for cytokeratin 7 of the oesophageal tumour showed diffuse positive stain of the oesophageal tumour cells. Immuno-histochemical staining for cytokeratin 7 of the metastatic bladder cells depicted positive staining of the tumour cells similar to the staining obtained in the oesophageal tumour.

Metastatic prostatic carcinoma does rarely occur but this is usually associated with malignant bladder neoplasms metastasising to the prostate. Marlin and associates [17] reported the case of a 73-year-old man with a history of gastro-oesophageal adenocarcinoma and clinically symptomatic benign prostatic hyperplasia who underwent photo-selective vaporization of the prostate and who presented several months later with visible haematuria, intermittent urinary retention and bilateral ureteral obstruction causing acute renal failure. After relieving the ureteral obstruction, trans-urethral resection of the prostate was performed and histological examination of the resected prostate revealed locally invasive metastatic oesophageal adenocarcinoma similar to the original oesophageal adenocarcinoma. Marlin and associates [17] stated that their case was the first case of gastro-oesophageal carcinoma to the prostate. To the knowledge of the authors no other gastro-oesophageal carcinoma metastatic prostatic carcinoma has been reported in the literature.

Van Lanschot and associates [18] stated that surgical resection of oesophageal adenocarcinoma of curative intent is associated with overall tumour recurrence rate of 66% at five years. Hulscher and associates [19] stated that the lymphatic drainage of the oesophagus is longitudinal via the sub-mucosal plexus and not segmental and as a consequence lymph node metastases can develop relatively early in all three compartments (abdomen, chest and neck) irrespective of the location of the primary tumour in the oesophagus. Sons and Borchard [20] observed from autopsy studies that isolated lymph nodes metastases were found in about one half of patients with end-stage oesophageal carcinoma and a similar proportion had combined lymph node and visceral metastases. They also observed the rarity of isolated visceral spread which accounted for only a handful of cases of primary oesophageal tumour spread.

Van Lanschot and associates [18] reported that sites where haematogenous dissemination of primary oesophageal carcinoma to distant organs, were reported include: bone, liver, skin, lungs, adrenal glands, brain and peritoneum in descending order of frequency. A number of authors most commonly in Japan have reported cases of oesophageal carcinomas metastasising to the kidney. These cases of oesophageal carcinomas metastasising to the kidney may present with haematuria but they are often associated with flank pain [21] [22] [23] [24] [25] [26] [27].

In addition, Goel and associates [28] reported a case of bilateral ureteric and renal pelvic invasion by metastatic esophageal carcinoma. They reported a fifty-year-old man who presented with oligo-anuria who was in renal failure and who required emergency haemodialysis because of hyperkalaemia and fluid overload. He had a post-dialysis infusion urography which revealed only faint nephrogram in the left kidney. He suddenly developed massive gastro-intestinal bleeding and died after 48 hours of hospitalisation. Autopsy revealed a flat ovoid growth, 8 cm x 3 cm, which involved the upper and middle third of the oesophagus which was totally obstructing the lumen. There was a greater sub-mucosal extension than the trans-mural infiltration. A satellite growth of 3 cm x 2 cm was found in the lower third of the oesophagus. Histological examination revealed a poorly differentiated squamous cell carcinoma. There was extensive spread in the retroperitoneum with tumour invasion of the back muscles and soft tissues. There was trans-capsular extension of the tumour involving the renal cortex, medulla and renal pelvis bilaterally. The tumour was of the same morphology as the oesophageal carcinoma. Both ureters were markedly thickened throughout their length with narrowing of the ureteral lumen. There was tumour invasion of all layers of the ureter. Both adrenal glands showed tumour metastasis. The pancreas also contained tumour of similar morphology within lymphatic spaces. The peri-pancreatic, mesenteric, paracolic and mediastinal

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lymph nodes contained tumour metastasis. The liver showed non-specific reactive hepatitis and was microscopically free of free of tumour. The lungs showed microscopic foci of tumour metastasis. The brain, the heart and spleen were normal. The prostate showed benign hyperplasia.

Furthermore, rare synchronous primary tumours of the urinary bladder and oesophagus have been reported [29] [30]. Matsumoto and associates [31] reported a case of a metastatic intra-pelvic tumour arising from oesophageal cancer. They reported a 74-year-old man who presented with gross visible haematuria. He had magnetic resonance imaging and cystoscopy which revealed a huge intra-pelvic tumour which invaded the bladder, rectum, sigmoid colon and ilium. The patient underwent total pelvic evisceration with ileal conduit and colostomy formation. The pathological diagnosis of the intra pelvic tumour was moderately differentiated squamous cell carcinoma. Pre-operatively, gastro-intestinal fiberoscopy revealed an oesophageal tumour which was biopsied and the histological examination of the tumour revealed moderately differentiated squamous cell carcinoma. The final histological diagnosis which was made after comparing the histology of the oesophageal tumour and the pelvic tumour was metastatic tumour from primary oesophageal cancer.

Some authors [32], [33] have stated that pure primary signet-ring cell carcinomas of the urinary bladder are very rare and only a few case reports exist of a mixed urothelial/signet-ring cell variant. Primary signet-ring carcinoma of the urinary bladder was first described by Saphir in 1955 [29] and since then less than 200 cases have been reported in the literature. Some authors have stated that there is a male preponderance of signet ring cell carcinomas of the bladder [2], [35], and the median age is 58 years [2]. Torenbeek and associates [36] stated that signet-ring cell carcinoma of the urinary bladder is far more common in men than in women with a male to female ratio of 11:2

Some authors iterated that signet-ring cell carcinomas of the bladder are very aggressive tumours with poorer survival [3], [35**]**. It has also been stated that the presence of a few signet-ring cells does not affect the prognosis of a bladder adenocarcinoma.

Some authors **[**5**]** stated that nodular histiocytic hyperplasia is rare, one case of signet ring cell carcinoma in the lamina propria exists, signet ring cell carcinoma of bladder may have mild atypia and mitosis, and may stain (a) strongly positive for CD68 but negative for keratin.

Other authors [4] stated that cystectomy may be important for the improved survival of patients with signet ring cell carcinoma of the urinary bladder. Wang et al [37] stated that signet ring cell carcinoma of the urinary bladder is a rare entity and that recent case series of signet-ring cell carcinoma of the urinary bladder showed inconsistent results. Wang et al. [37] stated that a total of 103 signet-ring cell carcinomas of the urinary bladder were present in their data base from 2001 to 2004. In that time 14,648 cases of transitional cell carcinoma of the urinary bladder were diagnosed. They found that signet-ring cell carcinoma of the urinary bladder was more common in younger than in older than in older patients ($p<0.001$); signet-ring cell carcinoma of the urinary bladder more commonly presented with high-grade histology ($p<0.001$) and advanced stage disease ($p <0.001$). The 3-year cancer specific survival rate was 67.0% and 33.2% for transitional cell carcinoma of the urinary bladder and signet-ring cell carcinoma of the urinary bladder respectively. They also reported that on multivariate analysis there was an increased mortality risk in patients with signet-ring cell carcinoma of the urinary bladder versus transitional cell carcinoma of the urinary bladder (HR 1.42, 95% CI 1.03-1.97, $p < 0.001$). When only high grade cases of signet-ring cell carcinoma of the urinary bladder and transitional cell carcinoma of the urinary bladder were compared, the risk was still worse in signet-ring cell carcinoma of the urinary bladder (HR 1.430, 955 CI 1.035 -1.976, 0.03). When they compared only local stage of signet-ring cell carcinoma of the urinary bladder and local stage transitional cell carcinoma of the urinary bladder, the risk was worse in signet-ring cell carcinoma of the urinary bladder (HR 4.294, 95% CI 1.035-17.825, 0.045). Wang et al. [37] additionally stated that limited to patients who underwent cystectomy only, the difference in cancer specific survival disappeared (HR 1.289, 95% CI 0.771-2.155, 0.33). Wang et al. [37] concluded that even after adjusting for demographic, pathological and treatment factors, cancer specific survival was significantly worse in patients with signet-ring cell carcinoma of the urinary bladder than transitional cell carcinoma of the urinary bladder. Wang et al. [37**]** stated that further research into the biology of this rare tumour is required to explain the aforementioned results.

Aggarwal and associates in 2011 [38] stated that as a result of their rarity there is no structured

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clinical research into urothelial signet-ring cell carcinoma and optimal management of early and advanced cases of this rare tumour is unknown. A number of differing chemotherapy regimens have been reported to advanced disease in various case reports and series with variable responses and generally modest benefits.

Del Sordo and associates [39] stated that:

- Signet-ring cell carcinoma of the urinary bladder occurs in the middle age and the clinical presentation does not differ from most transitional cell carcinomas.
- The prognosis is frequently poor as at diagnosis it is often in an advanced phase.
- It is essential to distinguish primary signet-ring cell carcinoma from metastases, as different therapeutic strategies are often necessary.

Michels and associates [35] reported an 81-year-old Asian man who presented with obstructive lower urinary tract symptoms. Clinical examination revealed an indurated prostate and inguinal lymphadenopathy. He had computed tomography scan which revealed marked bladder wall thickening, an enlarged prostate, pelvic and inguinal lymphadenopathy, diffuse liver and bony metastases as well as normal appearing gastrointestinal tract. He also had isotope bone scan which confirmed wide spread osseous metastases. He underwent cystoscopy which did not reveal any mucosal lesion, however, there was evidence of significant bladder neck obstruction. Histopathological examination of the trans-urethral resection specimen revealed prostatic tissue with diffuse infiltration by large areas of signet-ring carcinoma interspersed with poorly differentiated urothelial carcinoma. Immunohistochemical staining of the tumour tissue was negative for prostate-specific antigen (PSA) and prostate-specific acid phosphatase (indicating the tumour was not of prostatic origin), strongly positive for cytokeratin (CK) 7/20/ carcinoembryonic antigen (CEA), and strong nuclear positive for caudal-related homeobox 2 (CDX2) and negative staining for CK5/6. A number of serum tumour marker studies were done which revealed the following results: normal serum PSA; normal serum Beta Human Chorionic Gonadotrophin (Beta HCG); elevated levels of carcinoembryonic antigen (CEA) – 12 micrograms/L, [upper limit of normal 4 micrograms/L]; elevated levels of carbohydrate antigen (CA) 19-9 – 160kU/L [upper limit of normal 36 kU/L]. His base line renal function was impaired with a calculated glomerular filtration rate of 42 mL/min. His liver function test was normal. He was commenced on combination chemotherapy of gemcitabine and carboplatin for TNM stage T4N2M1 poorly differentiated signet-ring cell adenocarcinoma of the urinary bladder. Pursuant to his first cycle of chemotherapy treatment, he progressed with worsening of obstructive urinary symptoms, enlarging left inguinal lymph nodes, worsening serum CEA and CA 19-9 levels and worsening liver function tests which included alkaline phosphatase, aminotransferase and alanine transaminase. He was next treated by radiotherapy and he received 2100 cGy in 3 fractions for local control. Pursuant to his radiotherapy treatment he received second line chemotherapy with capecitabine. His cancer related symptoms normalized after the second line chemotherapy treatment and his tumour marker levels as well as liver function tests also returned to normal. Follow-up computed tomography scan also confirmed significant shrinkage of the number and size of liver metastases, reduction in tumour-related bladder wall thickening and lymphadenopathy. Despite the apparent promising initial result, 9 months after he had commenced his first course of capecitabine he developed progressive disease. He received a further treatment of capecitabine and he initially responded well clinically as well as based upon his tumour marker assessments. Nevertheless, after his third cycle treatment he deteriorated rapidly with tumour related obstructive jaundice and he died as a result of liver failure 12 months after initial diagnosis of his tumour.

Some authors [40] [41] stated that the histogenesis of primary signet ring cell carcinoma in the bladder is not well understood, and include metaplasia of transitional cell carcinoma. Kunze et al. [41] stated that the histogenesis of nonurothelial carcinoma is difficult to understand, since the bladder is normally lined exclusively by transitional cell epithelium. Kunze et al [41] stated that in order to gain more insights into the pathogenesis of nonurothelial carcinomas, the morphology and immunohistochemistry of transitional cell carcinoma, mixed transitional cell and nonurothelial carcinomas, and pure nonurothelial carcinomas were comparatively studied. They stated that:

- Of papillary and of non papillary (solid) transitional cell carcinoma (overall incidence 6.8%), 4.8% and 15.4% respectively disclosed foci of altered cellular and architectural phenotypes, consisting of squamous epithelium,

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pseudoglandular formations, and true glands with or without mucus production.

- The diverse phenotypic variants develop obviously by a metaplastic process as a result of the well-known inherent potential of the urothelium to undergo several pathways of cellular differentiation.

- There is strong evidence that squamous cell carcinomas arise secondarily from a squamous metaplasia and adenocarcinomas from metaplastic glandular epithelium within pre-existing transitional cell carcinoma following complete carcinogenic transformation of the initially bland-looking metaplastic tumour cells.

- The metaplastic origin of non-urothelial bladder carcinomas is supported by immunohistochemical findings. The high molecular weight cytokeratin 34betaE 12 identifies tumour cells with squamous characteristics, which helps to explain the development of squamous cell carcinomas.

- Secretions of MUC5AC apomucin is assumed to play a central role in the histogenesis of nonurachal mucus-producing adenocarcinomas, including signet-ring cell carcinomas.

Kunze et al. [41] iterated that metaplastic phenotypic variants of transitional cell carcinoma should be recognized as distinct entities with the potential to transform into nonurothelial carcinomas and thus possibly implying a poorer clinical outcome than typical, uniform transitional cell carcinoma.

Michels and associates **[**35] stated that the treatment of signet-ring cell variants of carcinoma of the urinary bladder is not well defined in view of the rarity of the tumour. Some authors [42] [43] stated that cystectomy is indicated for localized disease and they also reported that prolonged progression free survival with intra-arterial platinum or methotrexate based chemotherapy with or without radiotherapy to control localized disease. Nevertheless, other authors have stated that there is no standard systemic chemotherapy regimen for advanced disease, which on the whole is considered chemotherapy resistant [32]

Michels and associates [35] stated that case reports of signet-ring cell carcinoma originating from a variety of primary sites but also adenocarcinomas of the bladder indicate similar experience in as much that responses, if encountered appear to follow 5 fluorouracil (5-FU)-based regimens [44], [45], [46].

Wong and associates [47] stated that:

- Surgical treatment options for primary signet-ring cell carcinoma of the urinary bladder include: (a) trans-urethral resection or (b) partial cystectomy for small tumours and radical cystectomy with urinary diversion for diffuse tumours.
- Radiotherapy and chemotherapy have also been used; nevertheless, they have limited success and are mostly used as adjuvant therapy to surgery

However, Ota and associates [48] as well as Hirano and associates [42] have published cases that described the use of arterial infusion of carboplatin to treat primary signet-ring cell carcinoma of the urinary bladder. Hirano and associates [42] reported complete remission lasting 44 months.

Grignon and associates [2] stated that in view of the fact that primary signet-ring cell carcinoma is an aggressive tumour most patients (up to 65%) tend to present with locally advanced disease. Iqbal and associates [49] stated that in patients with locally advanced primary signet-ring cell adenocarcinoma of the urinary bladder, surgery is not a cure, but should be considered for palliation along with urinary diversion.

Erdogru and associates [50] in 1995 stated that the 70 cases of primary signet-ring cell carcinoma of the urinary bladder which they found in the literature pursued a fulminant and mostly fatal course and that the neoplasms diffusely invaded the bladder wall without forming intraluminal growths and they could not be controlled by segmental resection, radiotherapy and chemotherapy alone or in combination.

Shinagawa and associates [51] stated that the appearance of numerous signet-ring cells without any other type of adenocarcinoma cells originating in papillary transitional cell carcinoma in a urine-smear is rare. They reported that the cytology from mucus-urine which they initially obtained by washing from a 69-year-old female revealed three different types of cells:

(1) numerous single signet-ring cell carcinoma-type cells,
(2) low grade transitional cell-type cells arranged in sheets, and

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(3) Intermediate-(transitional)-type cells with aspects of transitional cell carcinoma and adenocarcinoma (SRC carcinoma) and mucus in the background.

The latter two cell populations were retrospectively confirmed after histologic diagnosis of a primary papillary transitional cell carcinoma with glandular differentiation. They recommended that one should keep in mind that even a low grade papillary transitional cell carcinoma with glandular differentiation of the bladder can exhibit excessive signet-ring cell-type cells in urine.

In 1980 Braun and associates [52] reported a 45-year-old paraplegic man who was hospitalized and evaluated for recurrent haemorrhagic cystitis of 8 months duration. He underwent cystoscopy which showed diffuse mucosal oedema with hypertrophy of the mucosal folds and intense hyperaemia in the region of the trigone of the urinary bladder. The biopsy of the trigone showed small mucin-producing signet-ring carcinoma cells diffusely infiltrating the sub-epithelial stroma. A complete diagnostic work-up which was carried out to uncover the presence of an extra-vesical primary neoplasm was negative. A repeat cystoscopy which was performed two weeks later for mapping out the extent of the bladder carcinoma revealed a new ulcerated lesion which was located in the left lateral wall; the biopsy of this lesion proved the existence of infiltrating carcinoma. A total cystectomy with construction of an ileal loop conduit was performed. His post-operative recovery was uneventful. Histological examination of the radical cystectomy specimen revealed that the bladder wall was grossly involved with tumour which depicted small signet-ring cells in clumps as well as single cells, diffusely invading the entire thickness of the urinary bladder. The tumour cells were mucin positive and were morphologically similar to the small signet-ring cells characteristically observed in gastric carcinoma of the linitis plastic type. Follow-up of over three years and nine months since the time of surgery did not show any clinical or laboratory evidence of recurrence of the tumour in the pelvis or elsewhere. The patient had remained well and free of cancer in January 1981. Braun and associates [53] reviewed the five cases of primary signet-ring cell carcinoma that had been reported by then and found that the neoplasms pursued a fulminant course, diffusely invaded the bladder wall without forming intraluminal growths, and they could not be controlled by segmental resection, radiotherapy, and chemotherapy alone or in combinations.

With regard to pathogenesis of signet-ring cell carcinoma of the urinary bladder Braun and associates [52] made the ensuing iterations:

- Primary signet-ring cell carcinoma of the urinary bladder has been thought to arise from the totipotent cells of the transitional epithelium.
- The presence of solid nests of transitional cells (Von-Brunn's nests) within the sub-epithelial stroma is not uncommon in the bladder; their frequent association with recurrent inflammation of the mucosal lining of the bladder tends to support the view that these cells may result from proliferative invagination of the urothelium into the lamina propria evoked by chronic irritation. Subsequent cystic degeneration of these urothelial buds produces the characteristic cystitis cystica.
- "Cystitis glandularis" ensues when the transitional cells abutting the central cystic space of cystitis cystica become transformed into columnar cells and acquire capability for mucus production.
- Mostofi and associates [53], [54] stated that it seems highly plausible that the rare mucogenic adenocarcinoma of the urinary bladder develops from such metaplastic cells.
- Further loss of differentiation (dedifferentiation) results in the formation of small undifferentiated cells that accumulate mucin within their cytoplasm which results in compression of the nucleus to one side of the cells. – The signet-ring cell is so formed.
- Rupture of the mucin-distended glands or individual cells produces mucin pools that are characteristically observed in these neoplasms.
- Saphir [34] stated that Small cells with scant basophilic cytoplasm are often observed admixed with the signet-ring cells and have been thought to represent degenerated signet-ring cells which had lost their capacity to produce mucin with subsequent cytoplasmic shrinkage. [34]
- Some authors iterated that undifferentiated signet-ring cell carcinoma may evolve directly from the totipotent transitional cells without passing through the intervening stage of metaplastic columnar mucus-producing cells as seen in adenocarcinoma of the bladder arising from cystitis glandularis [54] [55].

Shringapure and associates [56] reported a 48-year-old man who presented with dull aching right loin pain of 3 months duration. He did not have haematuria. His routine blood tests and urine

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examinations were normal. He had the following investigations with their results reported as follows:

- Ultrasound-scan of renal tract, abdomen and pelvis which revealed right hydronephrosis with right peri-ureteric collection.
- Intravenous pyelography showed urinary extravasation from the right mid-ureter with right hydroureteronephrosis.
- Computed tomography scan of the abdomen showed right hydroureteronephrosis with urinary extravasation from the right mid-ureter with thickening of the right wall of the bladder.

He underwent cystoscopy which revealed a sessile tumour in the right lateral wall, for which trans-urethral resection biopsies were taken. Histology of the resected specimen showed signet-ring feature with abundant mucin and confluent necrosis with muscle infiltration. Immunohistochemistry of the specimen was positive for CK 7, CK 20, and HMW. An extensive search was done to exclude other sites of a primary tumour. Upper and lower gastrointestinal endoscopy were negative for any tumour. Serum carcinoembryonic antigen (CEA) was undetectable. Diagnostic laparoscopy of the abdomen also failed to pick up any tumour elsewhere. 18FDG-PET (fluoro-deoxy glucose-positron emission tomography) scan of the abdomen showed avid FD3 uptake in the bladder. He underwent radical cystectomy with ileal conduit construction. The resected specimen showed cords and strands of cells filled with mucin infiltrating up to the perivesical fat (pT3N0M0). He was given four cycles of cisplatin and gemcitabine combination chemotherapy. He was alive and free of any recurrence at his one-year follow-up.

Shringapure and associates [56] iterated that:

- One of the main problems in case of a primary signet-ring cell carcinoma of the urinary bladder is the exclusion of metastasizing primary tumour at any other site in the body and therefore the presence of a predominantly signet-ring cell component should lead to a thorough search to exclude primary tumour at any other site in the body.
- Patients with primary signet-ring cell carcinoma of the urinary bladder manifest with symptoms related to the urinary bladder, while other primaries present with secondaries to the urinary bladder.
- The presence of glandular metaplasia has long been associated with a risk of malignancy, especially adenocarcinoma of the bladder. Nevertheless, cystitis glandularis is a well-known response of the urothelium to chronic irritation and the relationship between cystitis glandularis and adenocarcinoma of the bladder is no longer accepted.
- Adenocarcinoma arising in the urachus must be distinguished from adenocarcinoma of the bladder as it can be managed with partial cystectomy whereas adenocarcinoma of the bladder mandates cystectomy.

Chuang-Gang and associates [57] reported a case of signet-ring adenocarcinoma in the urachus. Johnson and associates [58] proposed the criteria to classify a tumour as of urachal origin as follows:

(1) Tumour in the dome of the urinary bladder
(2) Sharp demarcation between the tumour and the surface epithelium and
(3) Exclusion of primary adenocarcinoma located elsewhere with spread to the urinary bladder.

Jung and associates [59] reported 2 cases of primary signet-ring cell carcinoma as follows:

- Case 1

A 35-year-old man was admitted with a history of painless visible haematuria. The results of his routine blood tests were normal but urinalysis revealed many red blood cells. Cytological examination of his urine specimen revealed atypical cells. He underwent cystoscopy which depicted a sessile tumour extending from the right lateral wall to the dome of the urinary bladder. Computed tomography scan showed a 4 cm mass with calcifications on the wall of the right side of the urinary bladder. No lymph node enlargement or distant metastases were shown. He underwent trans-urethral resection of the bladder tumour. Histological examination of the tumour showed a signet-ring feature, with abundant mucin, confluent necrosis, and calcification. A complete upper gastrointestinal and lower gastrointestinal endoscopic evaluations were undertaken, and these were normal and analysis of tumour markers was also normal. The tumour was therefore considered to be primary signet-ring cell carcinoma of the urinary bladder. The patient underwent radical cystectomy, pelvic lymph-adenectomy, and construction of an ileal conduit. Macroscopic examination of the specimen revealed a lesion which extended from the right lateral wall of the bladder to the dome and this measured 6.0 cm in diameter. Microscopic

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examination revealed that the tumour was composed of signet-ring cells with an abundant mucin pool which invaded the perivesical adipose tissue. The adjacent mucosa revealed cystitis glandularis. The histopathological staging was pT3bN1M0. He refused post-operative chemotherapy. He remained free of local recurrence and distant metastasis until 28 months after his operation. He presented at 34 months post-operatively with back ache, nausea, vomiting and constipation. He had isotope bone scan and computed tomography scan which revealed multiple metastases to the ribs, spine, pelvis and liver. He then received radiotherapy (3,000 cGy every 3 weeks) and adjuvant chemotherapy with the M-VAC regimen (methotrexate, vinblastine, Adriamycin, and cisplatin. The patient died at 37 months post-operatively.

- Case 2

A 57-year-old woman presented with a recent history of visible haematuria, urinary frequency and urgency. Analysis of her urine revealed microscopic haematuria. Her routine blood test results were normal. She underwent cystoscopy which revealed a whitish, sessile mass that extended from the anterior bladder wall to the dome of the bladder. Computed tomography scan of his abdomen and pelvis revealed an invasive tumour that extended to the anterior omentum and mesenteric fat. He underwent trans-urethral resection of the tumour. Microscopic examination of the resected specimen revealed almost entirely tumour cells with signet-ring cell features with abundant mucin. There were also some fragments of surface urothelium showing intestinal metaplasia. Primary tumoral site work-up was done with fluorodecoxy glucose-positron emission tomography (FDG-PET) scan, gastrointestinal endoscopic examination, and tumour marker analysis. The FDG-PET scan revealed a metastatic focus at the omentum. No other primary site was found. The serum levels of carcinoembryonic antigen (CEA) and cancer antigen 125 (CA 125) were 195 ng/ml (normal range <5 ng/ml) and 6577 U/ml (normal range <35 U/ml) respectively. She also underwent gynaecological evaluation which revealed no specific findings (normal). A diagnosis of primary signet-ring cell carcinoma of the urinary bladder was considered and the patient underwent partial cystectomy and planned adjuvant chemotherapy. During the operation peritoneal carcinomatosis was identified. The partially resected urinary bladder revealed a 3.5 cm solid mass which was composed of nests or lobules of signet-ring cells with dissecting mucin pools. The tumour cells were infiltrating the perivesical fat tissue. The tumour was staged as pT3bNoM1.The patient refused to have post-operative adjuvant therapy.

Sharma and associates [60] reported a 30-year-old man who was diagnosed as having carcinoma of stomach after histological examination of biopsy specimen taken from his prepyloric ulcer. He underwent a computed tomography scan which revealed a growth in the pylorus of the stomach without any evidence of metastasis or ascites. He underwent radical D2 partial gastrectomy with gastrojejunostomy, which was followed by six cycles of chemotherapy with Docetacel and Cisplatin. Histopathological examination was suggestive of a Signet-ring variant of a poorly differentiated mucosal adenocarcinoma. The patient progressed well initially after treatment, however, 2 years later he presented with weight loss and painless intermittent visible haematuria. He had ultrasound scan which showed a localized thickening in the antero-superior wall of the urinary bladder. He also had a computed tomography scan which was suggestive of a neoplasm in the dome and adjacent left lateral wall of the urinary bladder. The gastrojejunal anastomosis appeared to be normal. His serum CA-72.4 level of 32.61 U/ml [normal range 5.60 – 8.20 U/ml) was found to be elevated. He underwent cystoscopy which revealed multiple grape-like lesions on the dome and left lateral wall of the urinary bladder. He underwent trans-urethral resection of the growth in his bladder. Histopathological examination of the resected specimen revealed a poorly differentiated mucin secreting adenocarcinoma of the signet-ring cell type in the lamina propria. The tissue from the base of the tumour was free from the lesion. The patient received six cycles of chemotherapy with Oxaloplatin, Epirubicin, and Capecitabine. Pursuant to the completion of chemotherapy, the patient had been progressing well with no evidence of recurrence found at cystoscopy 5 months after he completed his chemotherapy treatment.

Some authors [61] have stated that the management of metastatic tumours in the urinary bladder from a gastric primary carcinoma is mainly with chemotherapy. They stated that although there are no standard chemotherapeutic regimens for metastatic gastric carcinoma, best survival results are achieved with a three-drug regimen containing 5-fluorouracil (5-FU), an Anthracyclin and platinum compound like Cisplatin.

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Kondo and associates [62] in 2010 reported their review of 21 cases of signet-ring cell carcinoma of the urinary bladder which were reported in the Occidental and Japanese Journals. They reported that in 13 patients (62%) the carcinomas were of urachal origin and 8 (38%) were of bladder origin. They reported that: The prognosis of signet-ring cell carcinoma originating in the bladder was poorer in comparison with signet-ring cell carcinomas that originated in the urachus. There was a 2-year survival of 40% for the bladder group and 70% for the urachal origin group of tumours.

They recommended that a radical cystectomy excision of adjacent tissues which might improve the prognosis in this fatal malignancy should be considered.

Akamatsu and associates [63] performed a comprehensive review and analysis of the characteristics of primary signet-ring cell carcinoma of the bladder cancer of 54 cases in Japan. They reported that:

- The median age at diagnosis was 61.2 years with male dominance (2.1).
- Among the cases 46% had stage IV tumours.
- The overall survival rate at 2 years was 43%. However, none of the patients with stage IV disease at diagnosis were alive at 2 years.
- Multivariate analysis revealed that tumour stage and elevated carcinoembryonic antigen levels were significant prognostic factors.
- Of the 8 patients who were followed up for more than 2 years and showed no evidence of recurrence, 7 were treated by either radical or partial cystectomy.

Conclusions

Haematuria may be the only apparent symptom of signet-ring cell carcinoma of the urinary bladder. Diagnosis of signet-ring cell carcinoma of the urinary bladder may be made when microscopic examination of the bladder tumour reveals signet-ring type cells with intracytoplasmic mucin, and this diagnosis could be confirmed by positive immunohistochemical staining for cytokeratin. It has been recommended that signet-ring cell adenocarcinoma should be limited to cases with 25% or more signet-ring tumour cells.

If a patient who had previously undergone treatment for carcinoma elsewhere presents with haematuria a high index of suspicion should alert the urologist and the pathologist to exclude the possibility of metastatic tumour affecting the urinary tract from a previously treated carcinoma from other sites away from the renal tract in addition to excluding primary urinary tract causes of haematuria.

If a signet-ring cell carcinoma of the urinary bladder is diagnosed then clinicians, radiologists and pathologists have the responsibility of determining if the tumour is primary or metastatic by ensuring that exhaustive investigations including (a) computed tomography scans of thorax, abdomen and pelvis; (b) upper gastrointestinal endoscopy; (c) lower gastrointestinal endoscopy; (d) pathologists review of the morphology and immunohistochemistry of the bladder carcinoma and its comparison with the morphology and immunohistochemistry of any previous tumour the patient may have had as well as taking into consideration the fact that dedifferentiation may occur in metastatic lesions and at times the morphology of the metastatic lesion may therefore not be exactly identical with the primary tumour which highlights the dilemma pathologists may sometimes face.

Signet-ring cell adenocarcinoma of the urinary bladder is generally an aggressive tumour which should usually be treated by means of radical surgery and combination chemotherapy.

There are anecdotal reports of use of systemic chemotherapy without surgery in the treatment of primary signet-ring cell carcinoma of the urinary bladder.

There is no universal agreement regarding the choice of chemotherapeutic regiment for the treatment of signet-ring cell carcinoma of bladder of primary or metastatic origin.

In view of the rarity of signet-ring cell carcinoma of the urinary bladder of primary or metastatic origin, clinicians need to conduct a multi-centric studies regarding the treatment of such tumours in order to further study the biological behaviour of the tumour and to arrive at a consensus opinion on the therapeutic approach as well as the best chemotherapeutic regimen to use with the aim of improving the prognosis of such an aggressive tumour.

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