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ABSTRACT

Transitional cell carcinoma (TCC) is associated with malignant tumors that arise from stem cells near the basement membrane of the epithelial bladder surface. Exposure of carcinogens to the urothelium leads to genetic alterations in cells, increasing the malignant potential. Of the different environmental exposures, cigarette smoke is considered the greatest risk factor in the development of TCC in the United States. Pathological tumor growth patterns are classified as papillary (most common), sessile/mixed, or nodular, with TCC often arising via the flat or papillary pathways. Most commonly, TCC involves the papillary pathway, with formation of a tumor projecting into the bladder lumen and possible invasion of the lamina propria and bladder muscle. Constitutional symptoms such as weight loss, fatigue, along with lower abdominal pain or bone pain are often indicative of metastatic disease and poor prognosis. Metastasis of TCC most commonly occurs to the lungs, liver, or bone. Metastasis to the peritoneum with abdominal ascites, however, is very rare. In our case, TCC with peritoneal carcinomatosis and ascites in a 48-year-old male smoker can be appreciated. Abdominal pain with nausea, weight loss, and hematuria lead to computed tomography (CT) scan, which depicted ascites, omental thickening, and soft tissue mass in the urinary bladder. Biopsy and pathologic cytology revealed high-grade TCC with papillary morphology. Transitional cell carcinoma with peritoneal carcinomatosis is a rare cause of bladder carcinoma. Poor prognosis is due to advanced disease stage, poor performance status, and metastasis. Effective treatment often cannot be initiated, because of the grim presentation.

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Keywords: Papillary tumor, Peritoneal carcinomatosis, Transitional cell carcinoma

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INTRODUCTION

Bladder carcinoma (BC) is the most common malignancy of the urinary system in the world today. In 2015, there were an estimated 74,000 new cases of BC in the United States alone, accounting for nearly 4.5% of all new cancer cases. As such, BC is the second most common malignancy after prostate cancer in

middle-aged and elderly men. Bladder carcinoma is further divided into distinct histologic subtypes, with urothelial (transitional cell) carcinomas being more prevalent than non-urothelial carcinomas. In the United States and Europe, transitional cell carcinoma (TCC) accounts for approximately 90% of all bladder cancers, as opposed to other areas of the world, where non-urothelial carcinomas predominate [1–3]. Risk factors for the development of TCC are directly correlated to environmental exposures to the urothelium. Painless hematuria is the most common presentation of TCC with other irritative voiding symptoms also often reported. Transitional cell carcinoma initially spreads locally, with metastasis most commonly occurring in the lung, liver, adrenal glands, and bone. Abdominal ascites or metastasis to the peritoneum (peritoneal carcinomatosis) from TCC is exceedingly rare. In this case report, we describe a unique case of TCC with peritoneal carcinomatosis and ascites, along with the regimen utilized for treatment.

CASE REPORT

A 48-year-old male with a 30-pack year smoking history was admitted with abdominal pain, nausea, and vomiting. He also complained of a 50-lb weight loss and gross hematuria over one-year period. For further evaluation, abdominal CT was done, revealing ascites and omental thickening (Figure 1). Additionally, peritoneal carcinomatosis was seen on axial MRI, as depicted by peritoneal enhancement (Figure 2). Pathologic cytology from large volume paracentesis did not show evidence of malignancy. Pelvic CT, however, showed a 6.6-cm soft tissue mass in the posterior urinary bladder. Transurethral resection of bladder tumor (TURBT) was performed and common iliac lymph nodes were identified as positive for malignant infiltration. Histological analysis of the tumor mass biopsy showed papillary architecture with a high degree of cellularity and a high number of mitotic figures (Figures 3 and 4). Diagnosis of high-grade papillary transitional cell carcinoma (TCC) was made. Immunohistochemical staining for further stratification of disease process revealed negativity in MOC-31, CDX-2, Ber-Ep4, and B72.3. CEA levels were noted to be normal.

Due to malignant invasion of the bladder wall, coupled with common iliac lymph node metastasis, and peritoneal carcinomatosis, the tumor was staged at pT4, pN3, pM1, denoting the tumor to be a stage IV TCC with peritoneal carcinomatosis. Subsequent bone scan showed increased uptake in lumbar spine and sternum. Chest X-Ray showed a left-sided pleural effusion. As a palliative measure, the patient was treated with chemotherapy consisting of gemcitabine and carboplatin due to poor performance status.

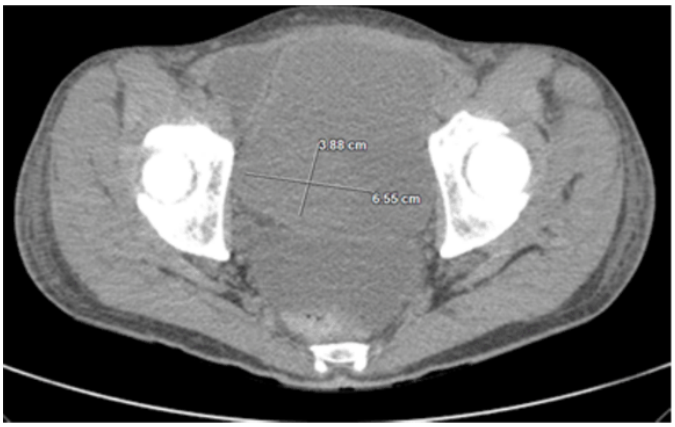

Figure 1: A posterior bladder soft tissue mass measuring 3.88x6.56 cm seen on axial computed tomography.

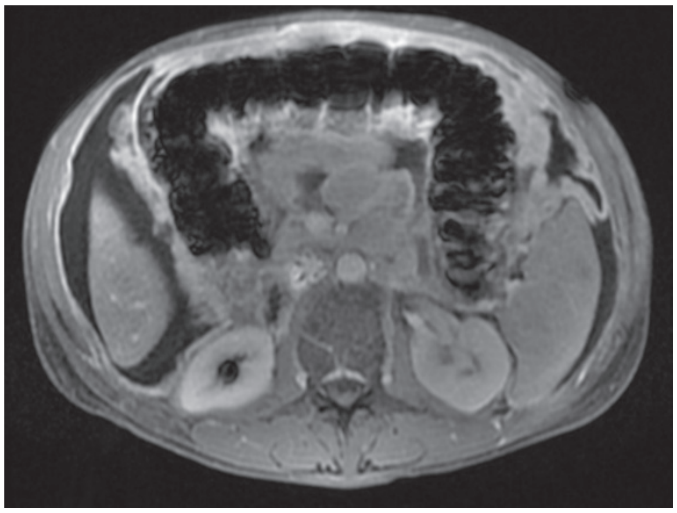

Figure 2: Peritoneal carcinomatosis is seen on axial MRI with peritoneal enhancement.

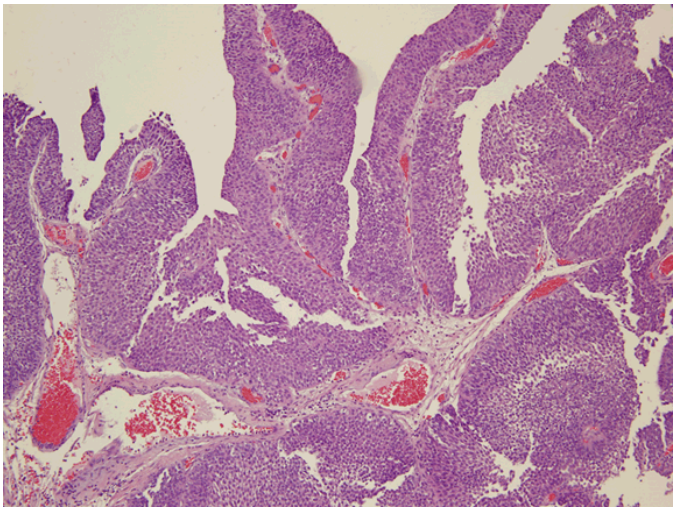

Figure 3: Papillary architecture with a high degree of cellularity and fibrovascular core of the bladder tumor mass biopsy (x4).

DISCUSSION

Transitional cell carcinoma (TCC) is the seventh most common malignancy in men and 17th most common

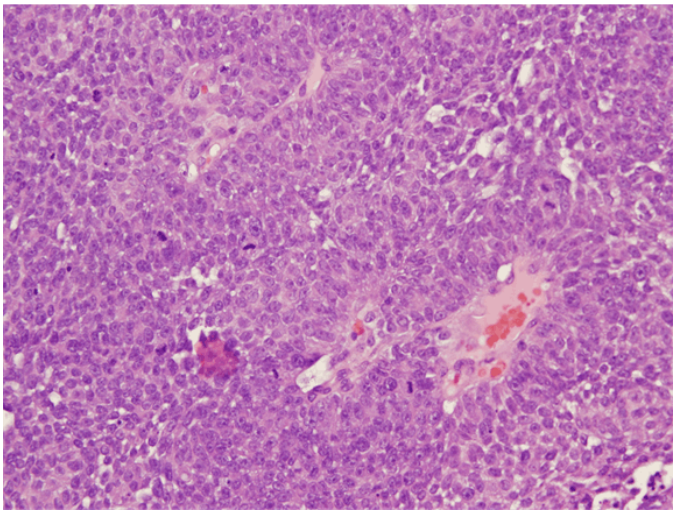

Figure 4: Nuclear pleomorphism with prominent nucleoli from the bladder tumor mass biopsy. There is also a high number of mitotic figures (x40).

malignancy in women in the world today [4]. The rates of new TCC cases have been steadily decreasing in both men and women, and death rates have been relatively stable. Due to the higher survival rate in TCC, 90% of people with TCC are over the age of 55, with an average age at the time of diagnosis being 73. A greater incidence of TCC development is seen in men, with Caucasians being diagnosed twice as often as African-American or Hispanics [3].

Bladder carcinoma is divided into two distinct categories; urothelial and non-urothelial carcinomas. Further classification is based upon which cell type becomes malignant. The cell type incorporating the most common malignancy of the urinary system in the US is TCC. Transitional cells, when subject to continued chemical and environmental exposures, cause uncontrolled growth and formation of neoplastic changes [4]. Transitional cell carcinoma is considered to be a urothelial carcinoma, as TCC arises from the urothelial lining of the bladder. Risk factors for TCC include exposure to certain dyes and chemicals used in making leather goods, textiles, plastics, such as azo dyes and naphthylamine [1]. Other risk factors include prolonged cyclophosphamide or phenacetin use. The most significant risk factor in TCC, however, is smoking. Non-urothelial carcinomas include squamous cell carcinomas (SCC) and adenocarcinomas (AC). Schistosomal bladder carcinoma (SBC) can be both urothelial or non-urothelial. Squamous cell carcinomas grows as flat masses of interconnected cells that typically form due to prolonged inflammation and irritation, such as recurrent UTIs, bladder stones, and pelvic radiation therapy [5]. Squamous cell carcinomas accounts for 3–5% BC in the US, and 75% of BC where *Schistosoma hematobium* infection is endemic. Adenocarcinomas, on the other hand, comprise less than 2% of non-urothelial BC cases. Adenocarcinoma is divided into two subcategories; urachal carcinomas (UC) and non-urachal carcinomas (NUC). Urachal carcinoma occurs secondary to a patent urachus with possible involvement of the urothelium. Prognosis of UC is greater than that of NUC, as it is less likely to be high grade. Non-urachal carcinoma, however, incorporates a worse prognosis due to a greater propensity for higher grade and metastasis. Non-urachal carcinoma tumors are often papillary or flat-infiltrating, commonly with muscle invasion. Schistosomal bladder carcinoma can be associated with UC or NUC, along with TCC, as it can give rise to all BC types.

Spread of malignancy to the peritoneum most commonly involves cancers of the ovaries, colon, or stomach, but spread from TCC of the bladder to the peritoneum is quite rare. According to Pevarski et al. [6], extensive peritoneal thickening and omental caking can indeed occur with TCC, albeit rarely. As such, importance must be placed upon consideration of TCC with peritoneal carcinomatosis as a differential when metastasis of malignancy presents in the peritoneum. To further describe peritoneal carcinomatosis in TCC, Turkbey et al. [7] studied 384 patients diagnosed with urinary BC. Computed tomography scans of 105 of the patients were reviewed for peritoneal implants, ascites, solid organ metastases, and retroperitoneal lymphadenopathy. Of the 105 patients in whom CT scans were reviewed, analysis of data revealed eight patients with findings of peritoneal metastasis (7.6%) and five patients depicting diffuse peritoneal involvement. Prognosis of those with peritoneal carcinomatosis was concluded to be poor. This is confirmed by Saxman et al. [8], who related that the performance status and presence of visceral metastasis are the strongest prognostic factors in TCC. In our specific case, the unique presentation of TCC with peritoneal carcinomatosis and ascites could be appreciated. Pathologic evaluation of histology revealed papillary architecture with a high degree of cellularity and fibrovascular core. Additionally, nuclear pleomorphism with prominent nucleoli and numerous mitotic figures were distinguished, suggesting TCC. Axial MRI scan depicted thickening of the peritoneum, further demonstrating metastasis of TCC to the peritoneum.

Although a majority of patients with TCC do not progress to advanced disease, 25% of patients have muscle-invasive disease that either present with metastasis, or later develop metastasis [9]. A five-year survival rates with multi-agent chemotherapy in this subpopulation is nearly 15 months, precipitating a poor prognosis. An appreciation of prognostic factors is imperative to determine which patients may benefit from chemotherapy. Clinical factors, such as poor performance status and the presence of pulmonary, liver, or bone metastasis directly correlate with decreased overall survival in clinical trials [9]. Saxman et al. [8] illustrated this in an Intergroup trial, which compared cisplatin alone versus methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) therapy. In this trial, it was found that the presence of liver or bone metastases along with poor

performance status was associated with a median survival of four months, as compared to 18 months in patients without these features. Apart from clinical factors, molecular abnormalities, such as mutations of p53 gene and mutations in DNA repair genes, are currently being reviewed as potential prognostic factors of survival in TCC with metastasis. Although treatment of metastatic TCC is still largely under research, it is agreed that cisplatin-based combination chemotherapy regimen is the preferred initial treatment [8]. Different formulations for treatment include MVAC, gemcitabine plus cisplatin (GC), and paclitaxel, gemcitabine, plus cisplatin (PGC). For patients who cannot tolerate cisplatin-based regimens due to impaired renal function and poor performance status, carboplatin-based therapy with gemcitabine is preferred. In the EORTC 30986 study by Santis et al. [10], carboplatin/gemcitabine therapy (CG) was compared to methotrexate/carboplatin/vinblastine therapy (MCAVI) therapy. It was concluded that CG therapy was as effective as MCAVI, but with a better toxicity profile. In our case, due to the advanced stage of TCC, coupled with peritoneal carcinomatosis and poor performance status, CG therapy was initiated as a palliative measure.

CONCLUSION

Transitional cell carcinoma with peritoneal carcinomatosis is an uncommon cause of bladder cancer, and generally has an unfavorable prognosis. The poor outcome is due to advanced disease stage, poor performance status, and metastasis, precluding effective treatment. In the case of our patient, transitional cell carcinoma with peritoneal carcinomatosis was identified after biopsy, histology, and immunohistochemical evaluation, uncovering a papillary morphology of the high grade tumor. Despite the lack of adequate research done on metastatic transitional cell carcinoma, our patient was started on carboplatin/gemcitabine therapy as a palliative measure. Transitional cell carcinoma with peritoneal carcinomatosis is a progressive disease with a poor five-year survival rate. As such, it is imperative to not only provide palliative treatment, but also psychological support for these subsets of patients.

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Author Contributions

Manraj Khosla – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Ali Imran – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Panagiotis Fidias – Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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