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Research Article

PRIMARY SIGNET RING CELL CARCINOMA OF URINARY BLADDER – A RARE CASE WITH RARE PRESENTATION

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ABSTRACT
Primary Signet Ring Cell Carcinoma (PSRCC) is a rare and aggressive variant of adenocarcinoma of urinary bladder which has a very poor prognosis. As compared to primary origin, metastasis of signet ring cell carcinoma(SRCC) from other sites or from urachus is more common in urinary bladder. Also, immunohistochemistry (IHC) is not very helpful in differentiating primary from metastatic SRCC as most of the markers used are overlapping. Therefore, a thorough search for primaries from other sites is must. It usually effects elderly males and presents mostly with hematuria and raised CEA levels. Radical cystectomy is the only therapy when tumor is localized. However, because of rarity of this tumor treatment options for invasive PSRCC are not well defined. We report a case of PSRCC which had a rare presentation i.e it affected a young female who complained of only irritative bladder symptoms and no hematuria and had normal CEA levels. IHC profile of this tumor was misleading. PET Scan and GI endoscopy was done to rule out metastatic SRCC. This tumor showed extensive loco regional spread to uterus and ovary and thus was treated with radical cystectomy, hysterectomy, oophorectomy and adjuvant chemotherapy. This case is reported here for its rarity, diagnostic dilemma and aggressive behavior.

Key Words: *Primary Signet Ring Cell Carcinoma (PSRCC), Signet Ring Cell Carcinoma (SRCC), Urinary Bladder (U.B), Adenocarcinoma, Chemotherapy*

INTRODUCTION

Primary Signet Ring Cell Carcinoma(PSRCC) of urinary bladder(U.B) is an extremely rare variant of U.B adenocarcinoma constituting approximately 0.24% of U.B malignancies.(Hamakawa *et al.*, 2013) It presents at an advanced stage and bears a poor prognosis (Yamashitaa *et al.*, 2014). The patient is usually an elderly male and clinical course is aggressive with a reported mean five year survival rate of 27-30%. One quarter of patients showed distant metastasis at first presentation and 60% died within one year (Hamakawa *et al.*, 2013). The diagnosis of PSRCC of U.B is difficult as studies detailing its Immunohistochemistry(IHC) profile are lacking and an exhaustive workup to rule out more common metastatic adenocarcinoma from other primary sites is required(Armache K *et al.*, 2014). Also, apart from radical cystectomy, no standard adjuvant chemotherapy regimen is available for PSRCC (ArmacheK *et al.*, 2014). We report a case of PSRCC in a young female from India who presented with only irritative voiding symptoms and no hematuria.

CASE

A 32year old female presented with complaints of burning micturition since 1month, pain abdomen after micturition since 1year, a history of loss of appetite, weakness and significant weight loss. There was no history of hematuria. Serum CEA and CA19.9 level were within normal range. Serum LDH was markedly raised. A CT SCAN revealed 6.2 X 5.6mm mass in dome of U.B with extension into surrounding soft tissue. On cystoscopy this mass showed extension to uterus, right ovary and anterior abdominal wall. Pelvic lymph nodes were also enlarged. Intravenous pyelography ruled out involvement of urethral and ureteric orifices. Initially a partial cystectomy was done with hysterectomy, right oophorectomy, part of anterior abdominal wall resection and bilateral pelvic lymph node dissection. The cystectomy specimen was sent for frozen section wherein both lateral margins showed positivity for tumor cells and hence a radical cystectomy had to be performed.

On histopathological examination the U.B mass consisted of tumor cells with abundant vacoulated cytoplasm which was pushing the nucleus to one side. The nucleus showed varying degree of atypia. These cells were positive for mucicarmine stain [Figure 1]. Thus a diagnosis of Signet Ring Cell Carcinoma was made. This mass was infiltrating the entire U.B wall thickness, outer 1/3rdof uterine wall at the level of junction and right ovarian parenchyma and sub-capsular space. Lymphovascular and perineural invasion was present. U.B mass also showed necrosis and mucin lakes. The anterior abdominal wall resection specimen did not show infiltration by tumor cells. All 5 pelvic lymph nodes submitted were positive for metastasis.

To ascertain the origin of tumor cells an IHC panel was used. IHC demonstrated the tumor cells were positive for CK20 and CDX2 [FIGURE1] and negative for CK7, Uroplakin and WT1. Negative staining for WT1 ruled out primary from ovary. But, CK20 and CDX2 positivity favored gastro-intestinal tract (GIT) origin. So, a PET scan abdomen and GIT endoscopy were done which came out negative [Figure 2].

Hence, radiology, morphology and IHC findings confirmed the tumor to be a PSRCC of U.B only.TNM staging given was pT4bN2M0. Accordingly, adjuvant chemotherapy with paclitaxel and carboplatin was started. Till date patient has received 3cycles of chemotherapy and is tolerating chemotherapy well.

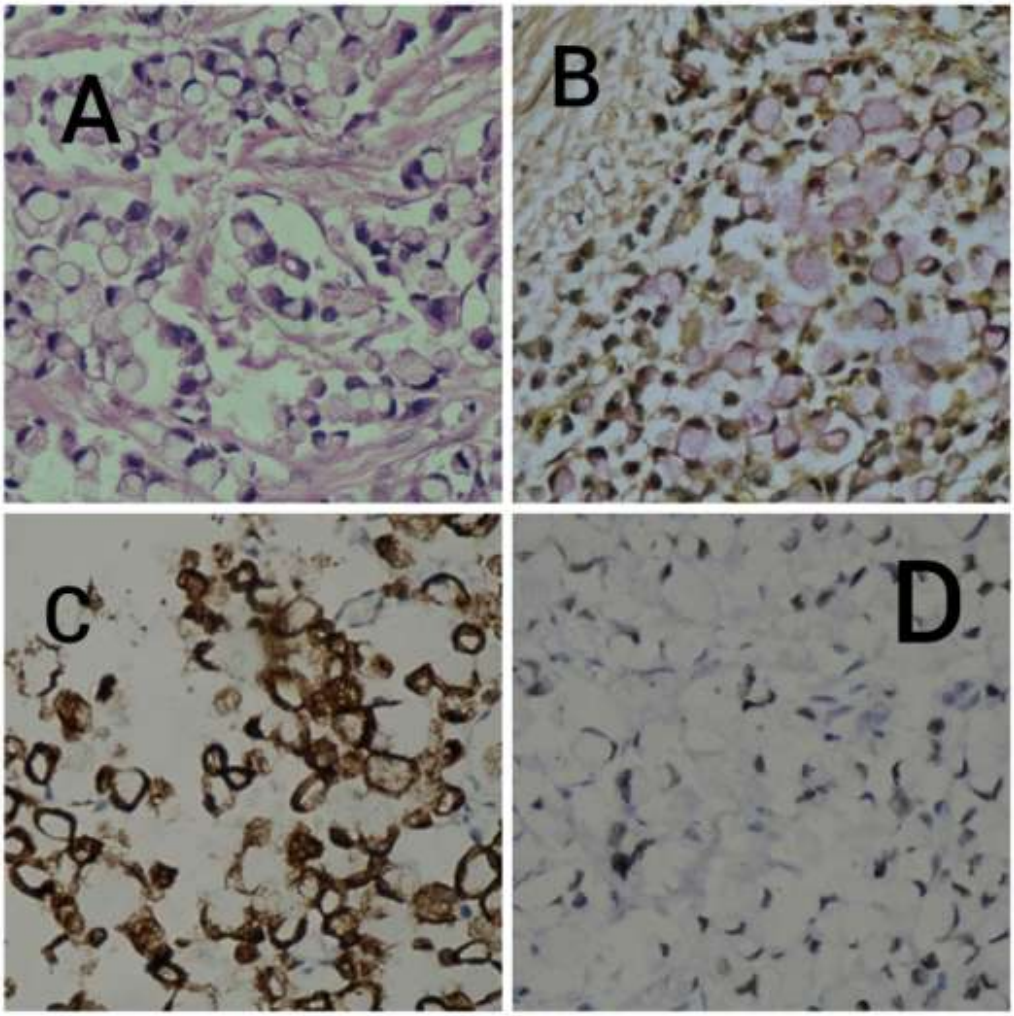

Figure 1: A-Tumor cells with signet ring cell morphology infiltrating UB wall (H&E, 40X)
B-Tumor cells are positive for mucicarmine stain (40X).
On IHC, tumor cells are positive for: C-CK20 (40X) and D-CDX2(40X)

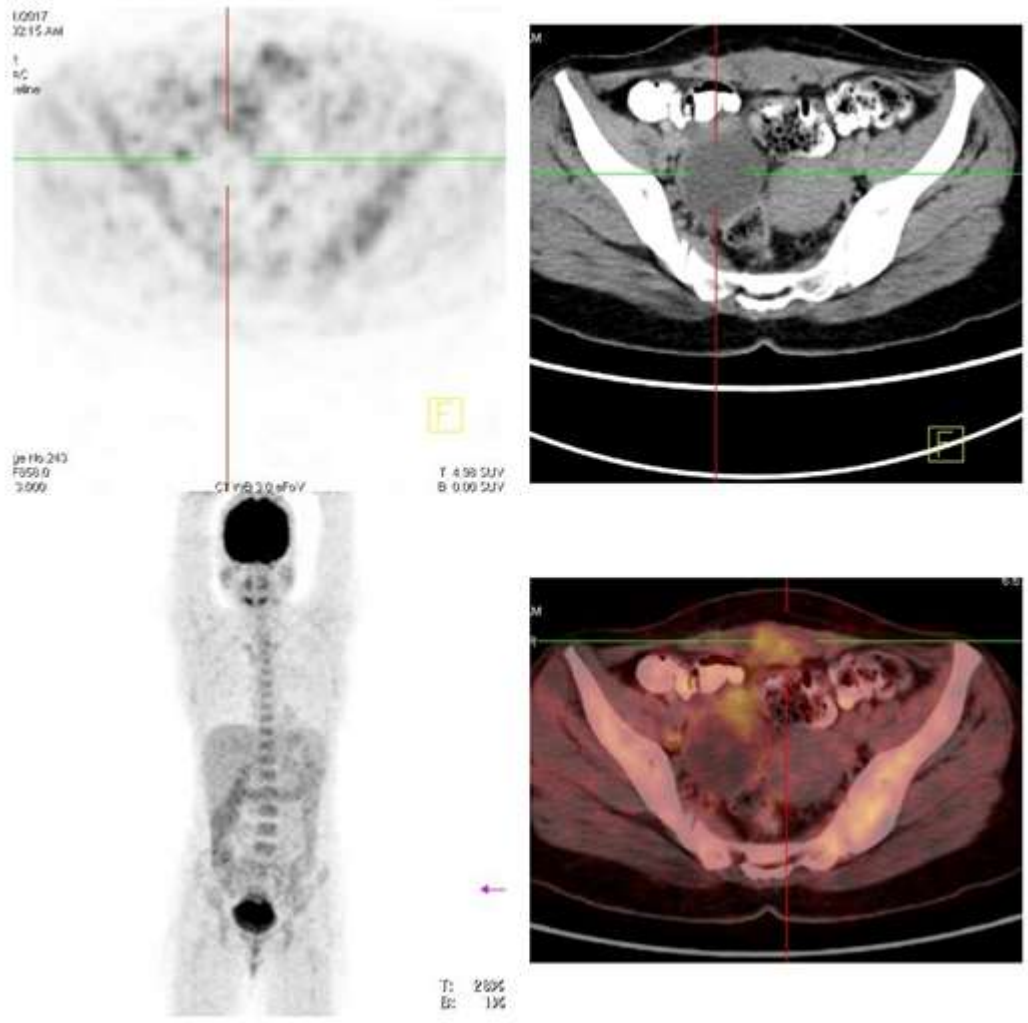

Figure 2: Whole Body PET SCAN images of the patient showing a urinary bladder wall tumor mass extending to uterine wall and right ovary and demonstrating an increased FDG uptake throughout the tumor. No growth or FDG uptake was noted elsewhere in the body.

DISCUSSION

PSRCC of U.B was first reported by Saphir in 1955. Less than 100 cases have been reported in literature so far (Armache *et al.,* 2014). Since U.B neither has columnar nor mucus secreting glandular epithelium, the histopathogenesis of PSRCC remains unclear. Theories proposed to explain it suggested origin from mesonephric remnants of trigone (Hamakawa *et al.,* 2013) or metaplasia in surface epithelium or in foci of cystitis cystica after chronic vesical irritation (Ammari JEE *et al.,* 2013).

The patients usually present in $7^{th}/8^{th}$ decade of life and there is male predominance (Shringarpure *et al.,* 2013). Our patient was unique in the fact that she was a young 32year old and a female patient. Also, hematuria is the most common presenting symptom in PSRCC (Shringarpure S*et al.,* 2013). But, even though our patient had irritative U.B symptoms since 1year there was no complaint of hematuria.

Among tumor markers, serum CEA level is documented to increase in PSRCC of U.B (Ammari JEE *et al.,* 2013) but in our case it was within normal range. Also, CA19.9 was within range giving a clue to an uninvolved GIT and pancreatico-biliary tract.

IHC showed positive staining for CK20 and CDX2 and negative for CK7 and Uroplakin which is also the IHC profile of GIT tumors. In the PSRCC of U.B case reported in one study (Allameh *et al.*, 2017), the tumor mass was positive for CDX2. But their case also co-expressed both CK7 and CK20 which is characteristic of urinary bladder neoplasm. So, our case presented with a diagnostic dilemma which has not been encountered in earlier reported cases in literature. We therefore performed GI endoscopy and PET SCAN abdomen to search for primary in GIT. No suspicious lesion was detected on both the investigations, hence metastasis from GIT was ruled out.

Origin from urachus was also suspected as the IHC profile was favoring distal gut origin. Johnson et al. proposed criteria to classify tumor as urachal in origin: (1) tumor in the bladder dome,(2) sharp demarcation between tumor and surface epithelium, and (3) exclusion of primary adenocarcinoma located elsewhere with spread to bladder (Shringarpure *et al.,* 2013). Although in our case the tumor was found to arise from U.B dome, but there was neither a sharp demarcation between tumor and surface epithelium nor the anterior abdominal wall resection specimen showed infiltration by tumor cells.

Metastasis from other sites which can have signet ring cell morphology are GIT, lungs and breast (Shringarpure *et al.,* 2013). These were also ruled out in our case with the help of a PET SCAN and GI endoscopy.

Radical cystectomy is the only therapy that offers possibility of a cure when tumor is localized. However, treatment options for invasive PSRCC are not well defined because of rarity of this tumor. Although combinations of methotrexate, vinblastine, doxorubicin, cisplatin or gemcitabine are standard chemotherapy regimens for treatment, PSRCC of U.B is generally resistant to these therapies and long term follow-up has shown considerable toxicity (Hamakawa *et al.,* 2013). Since in our case the tumor had already extended to uterus and right ovary, an extensive surgical resection in form of radical cystectomy, hysterectomy and oophorectomy was performed followed by an adjuvant chemotherapy with carboplatin and cisplatin. Till date patient has received 3cycles of chemotherapy and is tolerating chemotherapy well.

CONCLUSION

Primary Signet Ring Cell Carcinoma of Urinary Bladder is a rare and aggressive tumor which requires a multidisciplinary approach for its diagnosis. The diagnosis must be made only after thorough clinico-radio-pathological correlation. Even after a diagnosis is made, poorly defined treatment modalities makes the patient management difficult. Hence, only an early diagnosis and standardized treatment protocol can help improve its prognosis.

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