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RESEARCH ARTICLE

PRIMARY MUCINOUS ADENOCARCINOMA OF THE URINARY BLADDER: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Introduction: Primary mucinous adenocarcinoma of urinary bladder is an extremely rare disease. Symptomatically this tumor usually presents during the 5th and 6th decades of life with hematuria. It needs to be distinguished from mucinous adenocarcinoma metastasizing to the bladder from other primary sites. We report this case in a young man whose disease progressed to an advanced stage with minimal, irritative lower urinary tract symptoms and needed an extensive resection to achieve locoregional control.

Case Report: This 30 yr old male patient had been having irritative lower urinary tract symptoms for one year and had been under symptomatic treatment from traditional medicine practitioners. On evaluation he was diagnosed to have mucinous adenocarcinoma of bladder with extensive nodal metastases and a nonfunctioning right kidney secondary to uretero vesical junction obstruction caused by the tumor. He has been managed with radical cystectomy along with nephrectomy, ureterectomy and a super extended lymphnode dissection.

Conclusion: Adenocarcinomas of the bladder can present surreptitiously with minimal symptoms and no significant signs. A high index of suspicion is to be maintained while evaluating lower urinary tract symptoms. There should be a low threshold for ultrasound evaluation to avoid late diagnosis and morbidity. Mucinous Adenocarcinoma has an aggressive behavior and responds poorly to radiotherapy and chemotherapy.

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INTRODUCTION

Primary mucinous adenocarcinomas of the bladder is an extremely rare disease, despite the fact that tumors of the genitourinary tract are one of the most common cancers (Dadhania *et al*., 2015; Roy and Parwani, 2011; Youssef and Raj, 2011; Baffigo *et al*., 2012; Santos *et al*., 2015; Sigalas *et al*., 2010). Studies show that genitourinary cancers account for 20.79% of all cancers. In males genitourinary cancers comprise 17.48% of all malignancies, of these 40.71% are prostate cancers and 30.4% are urinary bladder cancers, making bladder tumors; the second most frequently encountered urological malignancy in males (Yuvaraja *et al*., 2016; Agarwal *et al*., 2016; Pan *et al*., 2016). The majority of bladder cancers are urothelial in origin. Primary adenocarcinomas of the urinarybladderare uncommon accounting for 0.5% to 2% of all vesical tumors. Primary mucinous adenocarcinomas of the bladder are a rare sub group of the above. These tumors are known to present at an advanced stage but, presentation with involvement of ureter, obstructive uropathy, ipsilateral non functioning kidney and extensive nodal disease is extremely rare. We report this case of a primary mucinous adenocarcinoma of the urinary bladder, involving right uretero-vesical junction, causing obstructive uropathy, loss of function of right kidney and extensive nodal disease. Primary adenocarcinoma of the urinary bladder often causes diagnostic confusion with adenocarcinomas metastasizing from adjacent and distant organs, like colon, rectum, prostate, ovary, uterus, lung and breast. Clinical, imaging, and histopathological correlation is mandatory before confirming the diagnosis. Mucinous Adenocarcinomas are aggressive cancers, with intramural growth, late onset of symptoms, delayed diagnosis and poor outcome. Radiation and chemotherapy have not been proven to be effective, and radical surgery remains the best therapeutic option (Dadhania *et al*., 2015; Youssef and Raj,

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2011; Baffigo *et al*., 2012; Sigalas *et al*., 2010; Pan *et al*., 2016; Zhang *et al*., 2012).

CASE REPORT

This 30-year-old shepherd presented with progressively worsening right flank pain, frequency of micturition and dysuria of one year duration. Though he had been reporting to various traditional medicine clinics for his symptoms, he was advised symptomatic treatment. It was only when his symptoms progressed significantly that an ultrasound examination of the abdomen was done and the patient referred to a larger center. At presentation the clinical examination including per rectal examination did not reveal any abnormality. Sonography of the abdomen showed a shrunken, hydronehrotic right kidney with thinning of the renal cortex, hydroureter, and a focal thickening of right lateral vesical wall (Figure 1). CT Scan of the abdomen revealed an irregular polypoidal lesion involving right posterolateral wall of bladder causing complete obstruction of the right vesico ureteric junction, dilatation of the right ureter, hydronephrotic shrunken right kidney thinning of renal cortex and extensive nodal metastases. A Diethylenetriaminepentaacetic acid (DTPA) scan revealed normal tracer flow and excretion by left kidney and a non functional right kidney. Cystoscopy revealed a polypoid wall thickening involving right posterolateral bladder wall obscuring the right uretero-vesical junction. Biopsy of the lesion revealed mucinous adenocarcinoma invading muscle. To exclude metastasis to the bladder from a primary at another site, a whole body FDG PET Scan was done. It revealed an FDG avid polypoid bladder wall thickening, with SUV max 11.06, involving the postero-superior wall of the urinary bladder and right uretero-vesical junction (Figure 2). The lesion had led to a non functioning, hydronephrotic, shrunken kidney with gross thinning of the renal cortex. FDG avid right obturator and iliac nodes were seen (Figure 3) along with paracaval and aorto caval nodes (Figures 4, 5, 6, 7) measuring upto 18.5mm x 15mm. No FDG avid lesions were noted in the neck, mediastinum, bowel, bones, lungs, liver, spleen and adrenals. A radical cystectomy with resection of the right ureter and the right kidney, with a super extended lymph node dissection achieving clearance of the pelvic, para caval and aorto-caval nodes, and a Bricker ileal conduit urinary diversion of the left kidney was done (Figure 8).

The tumor was resected with macroscopically clear margins. An extended lymph node dissection including the pelvic, para-caval, aororto caval and para-caval nodes up till the left renal vein was done (Figure 9). The Final HPE has been reported as Moderately Differentiated Invasive Mucin Secreting Adenocarcinoma of the Bladder (Figure 10). The Prostatic stroma showed tumor infiltration but the urethral cut margin was free of tumor. The PAS stain showed intacellular and exracellular mucin (Figure 11). Tumor metastases was seen in 11/15 dissected lymph nodes. Final pathological staging has been reported as pT4a (Tumor involving prostatic stroma), N3 (Lymph node metastasis to the common iliac nodes), M1(Lymph node metastases in distant lymph nodes). He was started on adjuvant chemotherapy and during treatment developed low back ache. Repeat PET CT has shown vertebral metastases. He is now planned for palliative RT.

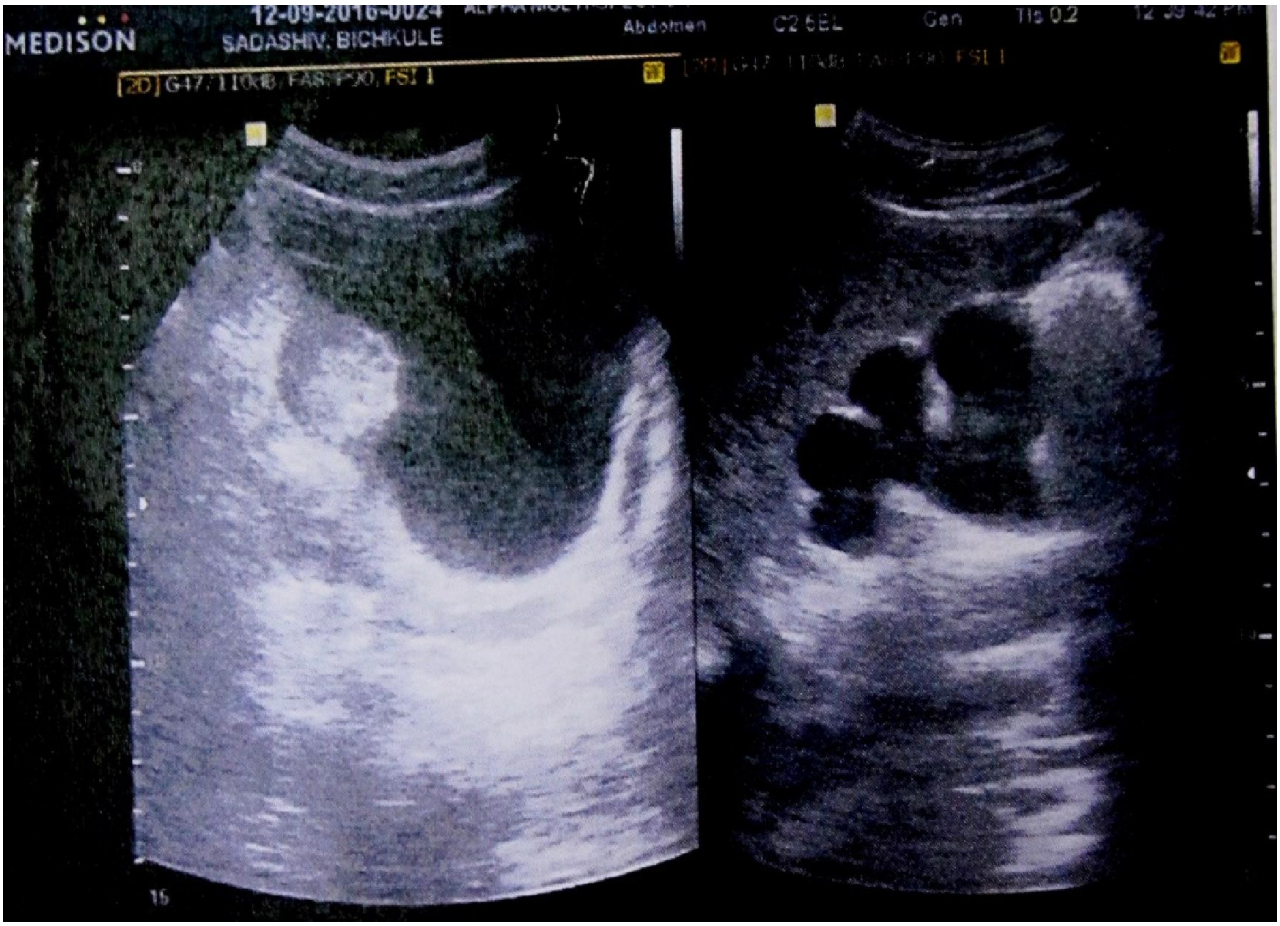

Figure 1. Ultrasound of the Abdomen showing a focal thickening of the right posterolateral vesical wall and the shrunken right kidney, with thinned out cortex and hydronephrosis

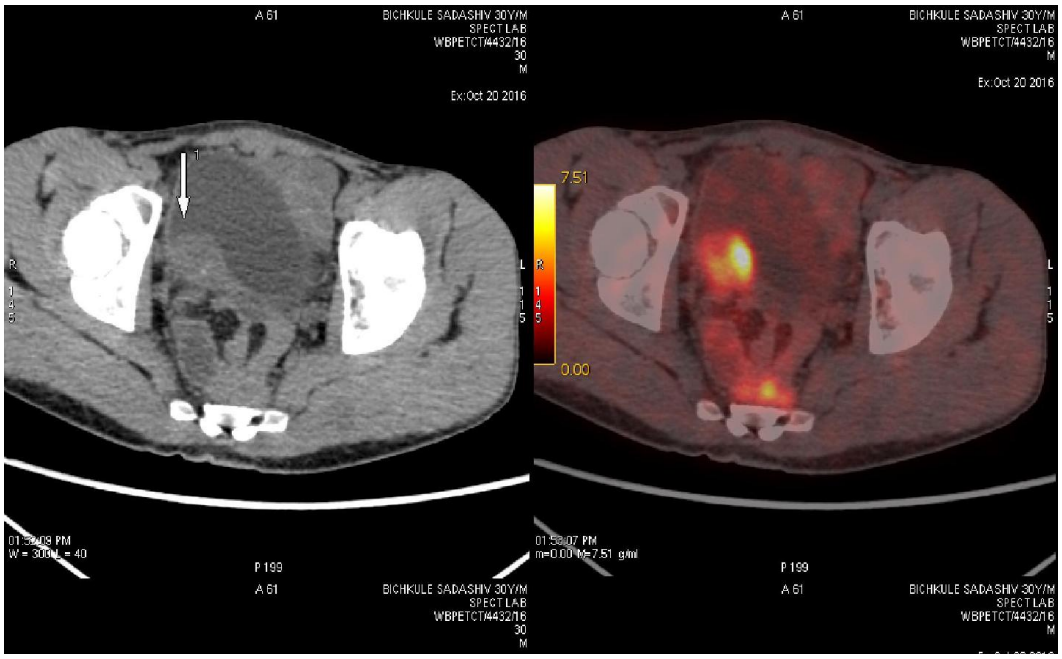

Figure 2. CT-PET scan showing lesion in the right posterolateral wall of the bladder

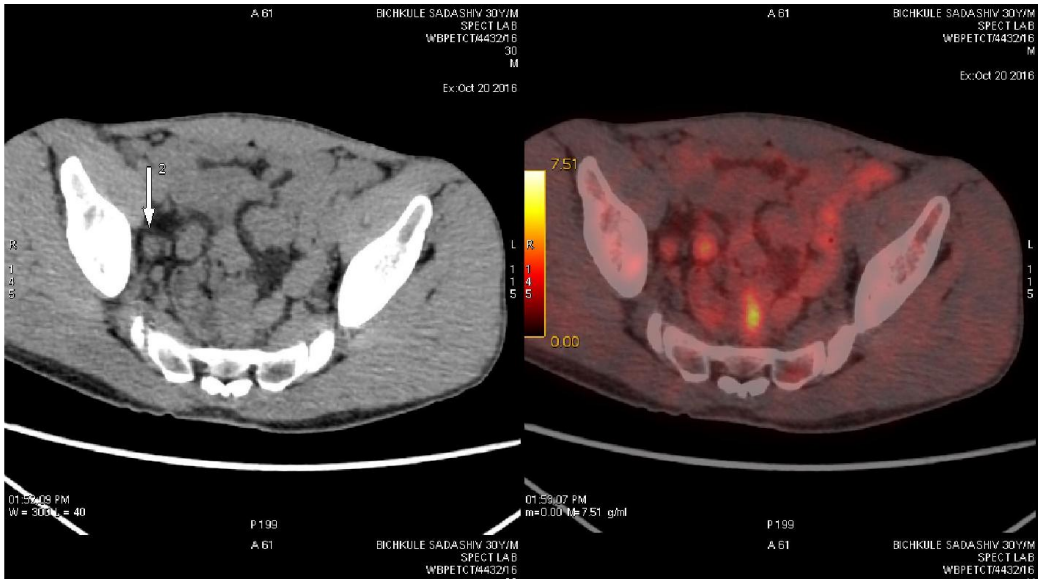

Figure 3. CT-PET scan showing hypermetabolic right obturator node

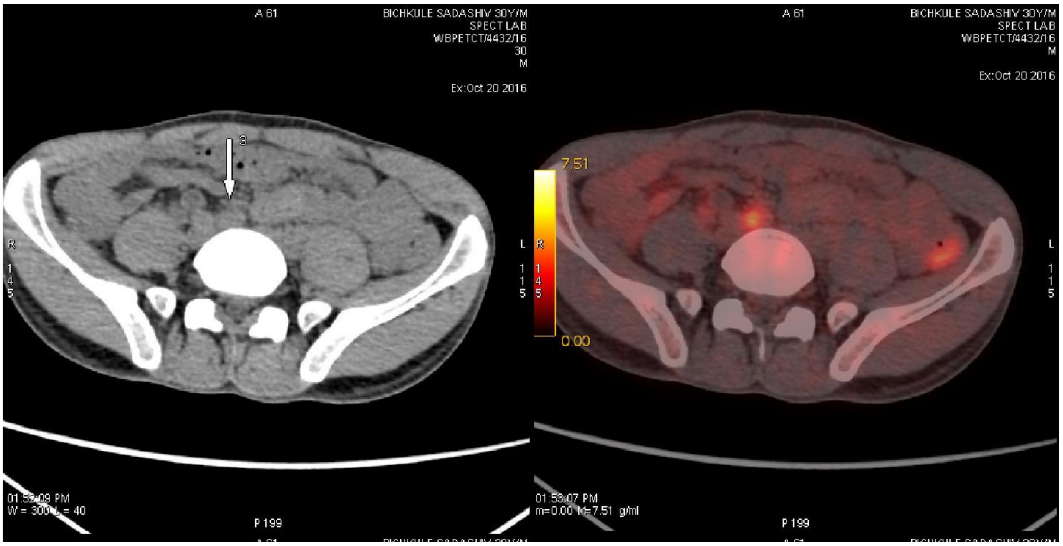

Figure 4. CT-PET scan showing hypermetabolic common iliac node

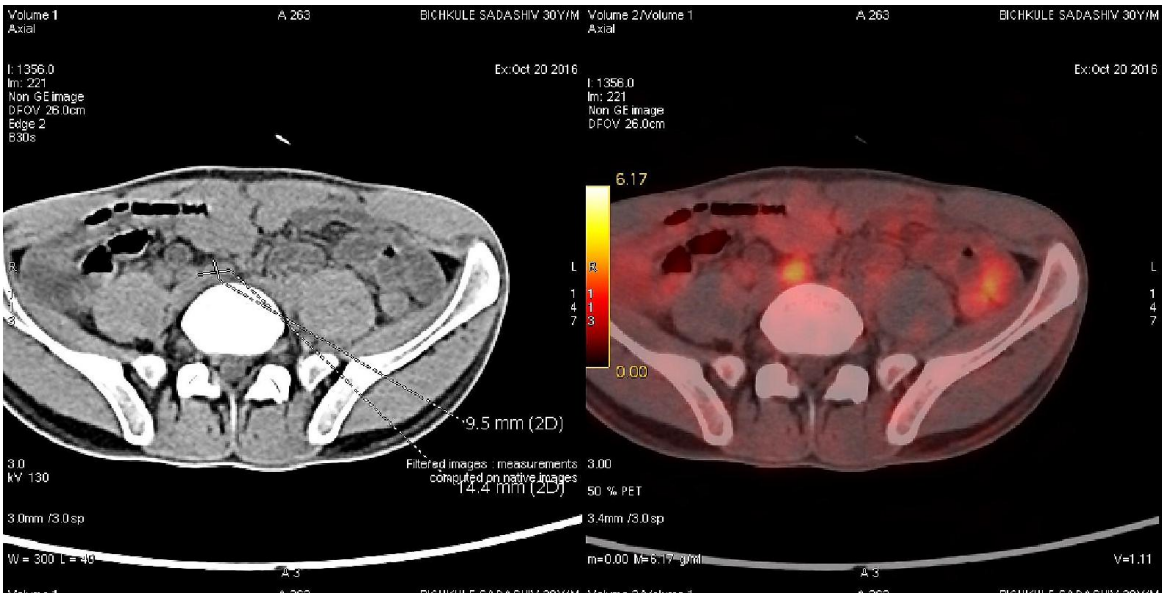

Figure 5. CT-PET scan showing hypermetabolic 14.4 x 9.5 mm lower aorto-caval node

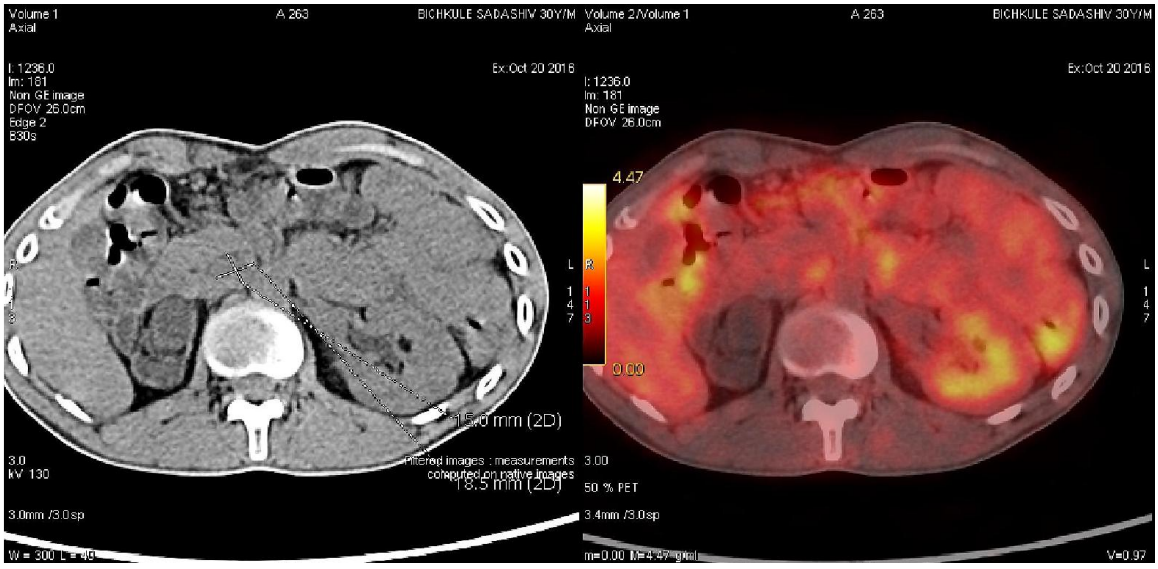

Figure 6. CT-PET scan showing 18.55mm x 15mm aorto caval node

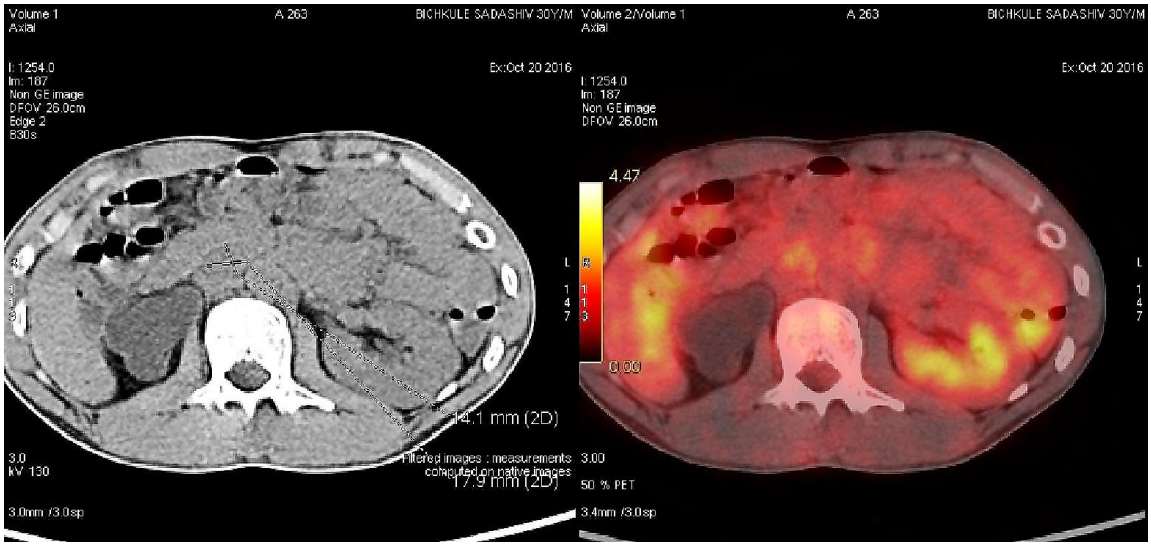

Figure 7. CT-PET scan showing NFK (R) and 17.9 mm x 14.1 mm aorto caval node

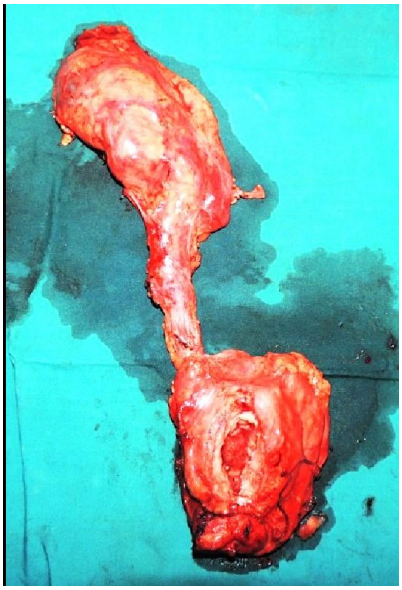

Figure 8. Resected right kidney, ureter and bladder

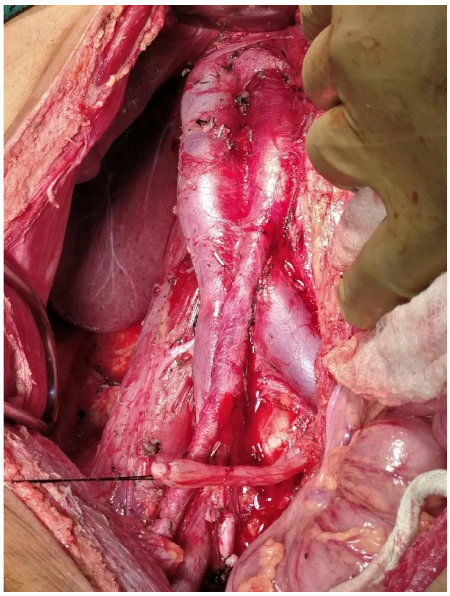

Figure 9. Field after right nephroureterocystectomy with super extended lymphadenectomy. Left ureter brought to the right

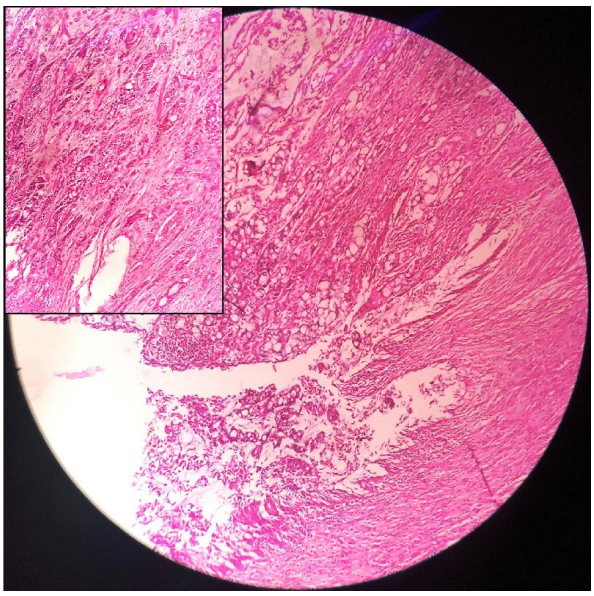

Figure 10. Photomicrograph showing mucin secreting adenocarcinoma originating in the mucosa (Inset shows the high power view)

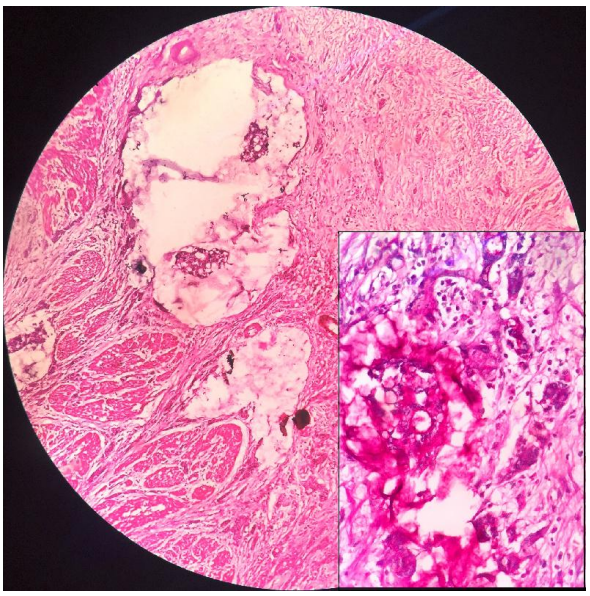

Figure 11. Photomicrograph of PAS stain showing intracellular and extracellular mucin (Inset shows the high power view)

DISCUSSION

Primary mucinous adenocarcinomas of the bladder are a rare entity, despite the fact that tumors of the genitourinary tract are one of the most common cancers encountered in clinical practice (Dadhania *et al*., 2015; Roy and Parwani, 2011; Youssef and Raj, 2011; Baffigo *et al*., 2012; Santos *et al*., 2015; Sigalas *et al*., 2010). Studies show that genitourinary cancers account for 20.79% of all cancers. In males genitourinary cancers comprise 17.48% of all malignancies and of these 40.71% are prostate cancers and 30.4% are urinary bladder cancers, making bladder cancers the second most frequently seen urological malignancy in males (Yuvaraja *et al*., 2016; Agarwal *et al*., 2016; Pan *et al*., 2016). Most of these tumors are urothelial cancers. Adenocarcinomas of the urinary bladder are rare accounting for only 0.5% to 2% of all vesical tumors and the primary mucinous adenocarcinoma of the bladder is extremely rare. They have appearances similar to adenocarcinoma of the gut. Several turn out not to be primary vesical lesions but are metastatic deposits from adenocarcinoma at others sites, commonly from colon, rectum, appendix, stomach, pancreas, lung, ovary, prostate, breast, uterus and cervix. The diagnosis of primary bladder adenocarcinoma should be made only after exclusion of secondary involvement by adenocarcinoma from other organs (Dadhania *et al*., 2015; Roy *et al*., 2011; Baffigo *et al*., 2012; Santos *et al*., 2015; Sigalas *et al*., 2010; Pan *et al*., 2016). Primary adenocarcinomas of the bladder are derived from the urothelium of the bladder but exhibit a pure glandular phenotype as was seen in our case. Several risk factors have been mentioned including, extrophy of the bladder, schistomiasis, chronic irritation, tobacco use and obstruction but these were not identified in this case. Bladder adenocarcinomas usually arise from the trigone and posterior

wall which is consistent with the findings in our case, the tumour blocked the right ureterovesical junction and caused loss of right kidney function. The location near the right ureterovesical junction and posterior bladder wall and the absence of identifiable urachal remnants within the tumor, excluded a urachal origin (Dadhania *et al*., 2015; Roy *et al*., 2011). The absence of detectable FDG avid lesions at sites other than the urinary bladder and draining lymph nodes, excluded a metastatic deposit of adenocarcinoma from a primary in another organ.

The presentation at 30 years of age, with only irritative lower urinary tract symptoms and secondary effects of tumor causing obstruction and loss of function of the kidney, are a variation from the usual presentation which includes presentation in sixth decade of life with hematuria along with lower urinary tract irritative symptoms (Dadhania *et al*., 2015; Roy *et al*., 2011; Baffigo *et al*., 2012; Santos *et al*., 2015; Sigalas *et al*., 2010; Pan *et al*., 2016). The absence of hematuria and debilitating symptoms for nearly a year allowed the tumor to progress, cause loss of right kidney function and involvement of distant lymph nodes. These tumors can arise anywhere in the urinary bladder but most cases show involvement of the trigone and posterior bladder wall and are usually single as in this case. In contrast the usual urothelial tumors tend to be multifocal. Cystoscopy usually shows a papillary, nodular, flat or ulcerated appearance, some variants present with prominent bladder wall thickening, without apparent growth due to diffuse infiltration of the bladder wall by malignant cells (Dadhania *et al*., 2015; Roy *et al*., 2011; Sigalas *et al*., 2010). The cut surface may have a gelatinous appearance because of abundant mucin production but was not noted in this case and the mucin was seen on histopathological examination and PAS staining. The enteric type of cancers are composed of intestinal type of glandular structures, pseudostratified columnar cells and nuclear atypia resembling colorectal carcinoma. The mucinous type as in our case; (Figures 10 &11) produces intracellular and extracellular mucin with tumor cells often floating in pools of mucin (Dadhania *et al*., 2015; Roy *et al*., 2011; Sigalas *et al*., 2010). The signet ring type is made up of diffusely infiltrating poorly differentiated cells with prominent intracellular mucin and indented eccentric nuclei. The not otherwise specified types have a non-specific glandular pattern. Hepatoid variants have a pattern mimicking hepatocellular carcinoma and express alpha feto-protein, Hep Par 1 and Alpha-1 antitrypsin, bile production can be seen. Clear cell adenocarcinoma is a unique variant of bladder carcinoma which affects women more than men. They are thought to be of mullerian origin and are often associated with endometriosis and mullerianosis (Dadhania *et al*., 2015; Roy *et al*., 2011). The typical colonic adenocarcinoma immunohistochemical staining profile of CK7 negativity and CK20 positivity has been reported in 29% of primary vesical adenocarcinomas and thus may not accurately distinguish between primary bladder carcinoma and metastatic colonic carcinoma. The same is largely true for other colonic markers leaving immunohistochemistry with a limited role in making this distinction. Immunohistochemistry is useful to identify metastasis from prostate using the PSA marker, CA 125 marker to stain tumors of endometrial and ovarian origin, Vimentin to highlight endometrial cancer cells as opposed to bladder carcinoma cells and estrogen receptor and gross cystic disease fluid protein 15 which stains breast cancer cells. In view of the limited role of immunohistocehemistry to make this distinction, clinical history, physical examination, colonoscopic findings, FDG PET CT scans have to be factored in to the histopathology report to make an accurate diagnosis (Dadhania *et al*., 2015; Roy *et al*., 2011). Florid Cystitis cystica et glandularis may mimic adenocarcinoma and is often seen in areas adjacent to the bladder adenocarcinoma but was not seen in our case (Dadhania *et al*., 2015; Roy *et al*., 2011; Sigalas *et al*., 2010).

The other distinction which needs to be made when faced with a diagnosis of adenocarcinoma of the bladder is to exclude urachal carcinoma which can present as a bladder mass. These tend to show a male preponderance and are usually located in the dome and anterior bladder wall, do not have associated cystitis cystica and cystitis glandularis, but show predominant invasion of the muscularis, sharp demarcation between the tumor and the bladder urothelium, identifiable urachal remnants within the tumor, involvement of the space of Retzius and anterior abdominal wall as well as no demonstrable primary at any other site (Dadhania *et al*., 2015; Roy *et al*., 2011; Pan *et al*., 2016). The location of the primary in the reported case, away from the dome and anterior wall suggests a non urachal origin. The prognosis varies with TNM stage at presentation, R0 resection, tumor grade and histological subtype. The high grade tumors, mucinous, signet ring cell and clear cell types behave particularly aggressively. Urachal and dome location of bladder adenocarcinoma is associated with a favourable prognosis, basal location confers a poorer survival and oncological outcome. Unfortunately, low stage bladder adenocarcinomas comprise less than 30% of reported cases; the majority present late (Dadhania *et al*., 2015; Roy *et al*., 2011; Santos *et al*., 2015; Sigalas *et al*., 2010; Pan *et al*., 2016; Zhang *et al*., 2012; Dutta *et al*., 2016; Zaghloul *et al*., 2006). Currently a two-track model of bladder cancer progression has been proposed, segregating the papillary and solid tumors. It is hoped that the identification of molecular and genetic markers, will help refine prognosis and plan therapy (Kang *et al*., 2014; McConkey *et al*., 2010). For the majority of patients, the main stay of treatment is surgery with or without radiotherapy and chemotherapy. Radical or partial cystectomy with or without node dissection is the usual surgical procedure (Dadhania *et al*., 2015; Roy *et al*., 2011; Youssef *et al*., 2011; Baffigo *et al*., 2012; Santos *et al*., 2015; Sigalas *et al*., 2010; Pan *et al*., 2016; Zhang *et al*., 2012; Zaghloul *et al*., 2006). Extended lymphnode dissections have been reported to provide better outcomes (Zehnder *et al*., 2011; Sundi *et al*., 2014; Bruins *et al*., 2014). In our case, radical right nephroureterocystectomy with an extended lymphnode dissection and a Bricker ileostomy was done. He was started on adjuvant chemotherapy, but developed backache. A follow up CT PET scan revealed vertebral bony metastases. He has now been scheduled for palliative Radiotherapy.

Conclusion

Primary mucinous adenocarcinoma of the bladder is a rare cancer with a wide variety of gross and microscopic appearance. It usually presents in older individuals, with hematuria and irritative bladder symptoms. Persistent bladder irritative symptoms, in the absence of infection and stone disease warrants a meticulous evaluation to detect these tumors. Metastatic deposits from gut and other primary sites needs to be excluded before confirming a diagnosis of primary mucinous adenocarcinoma of the bladder and mapping the extent of the tumor and clinical TNM stage. Since surgery is the most effective therapeutic modality, R0 clearance should be the aim. Adjuvant Chemotherapy and radiotherapy are to be

added based on histopathological report of the excised specimen and final pTNM staging. These may be offered up front if the disease is considered irresectable at presentation.

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