

Breaking the Age Barrier: Mucinous Adenocarcinoma of the Bladder in a Young Man

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ABSTRACT

Adenocarcinoma is a rare form of malignancy, representing approximately 0.5% to 2% of all bladder cancers. Approximately 90% of patients exhibit haematuria at presentation. The condition primarily affects adults, peaking in incidence during the seventh decade of life, with a higher occurrence in males. Tumors can develop throughout the urinary tract, including the bladder, urethra, renal pelvis and ureter. Due to its rarity, the underlying causes are not well understood. It has been postulated that bladder adenocarcinoma may result from malignant transformation of intestinal metaplasia in the urothelial mucosa. In our study we have diagnosed, A 24 year old male patient from West Bengal, who presented with tumor sized 3.8x3.5x3.5cm in the dome of bladder was diagnosed with primary invasive adenocarcinoma of bladder – mucinous type. The diagnostic challenge of this case that we had to thoroughly evaluate to exclude the primary from other organs like colon or prostate. Mucinous and signet-ring cell histological patterns are extremely rare, and they are often challenging to differentiate morphologically from metastatic colorectal adenocarcinoma. Careful correlation with clinical, radiological, biopsy, staging and immunohistochemistry plays a vital role in diagnosing such rare tumor. Stage is important prognostic factor. 5 year disease free survival rate is 40-50%. Treatment is radical cystectomy followed by adjuvant therapy with chemo or radiotherapy, after excluding gastrointestinal origin primary malignancy.

Keywords: Invasive Bladder adenocarcinoma, haematuria, immunohistochemistry

1. INTRODUCTION

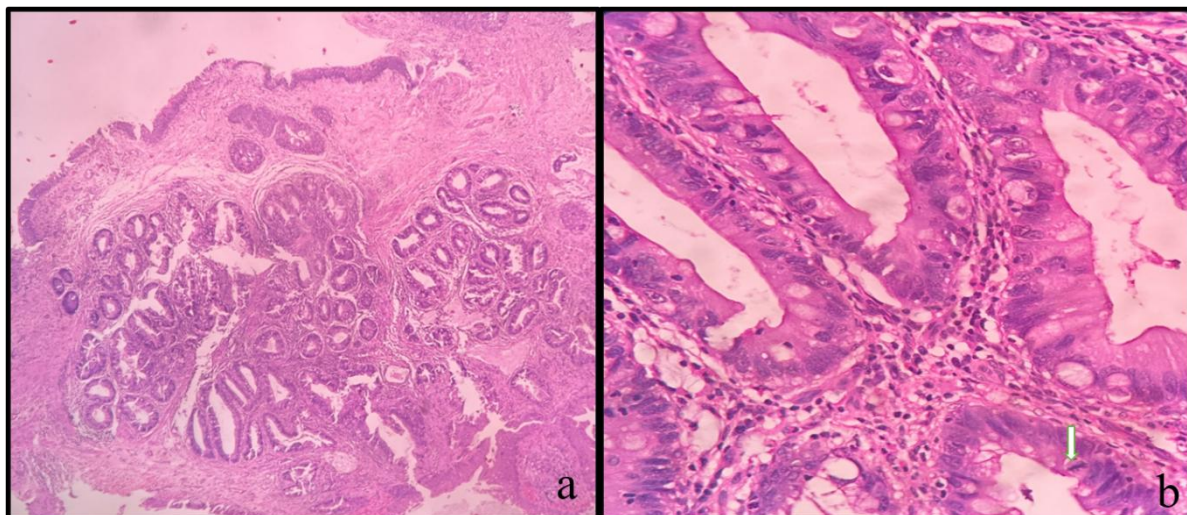
A 24 year – old male from west Bengal, accountant by occupation, non - smoker presented with one year history of painless gross haematuria on and off. Patient also complained of weight loss of 3 kgs in 2 months. No complaints of dysuria or urinary retention. No known comorbidities or significant family history. Physical examination revealed no abnormality.

Patient had undergone USG abdomen and pelvis which hypoechoic mass in the bladder measuring $\sim 4 \times 3.2 \times 3$ cm. Further CT urography done, which showed a well-defined, heterogeneously enhancing exophytic lesion seen arising from the anterior wall of urinary bladder adjacent to superior aspect, measuring $\sim 4.4 \times 3.5 \times 3.3$ cm (anteroposteriorly x transverse x craniocaudally). Prostate is normal in size and attenuation [Table/Fig-1]. MRI suggested irregularly enhancing mural nodule in the inferior aspect – projecting into urinary bladder lumen with discontinuity of urinary bladder wall - likely neoplastic change. No invasion noted into the adjacent structures or organs.



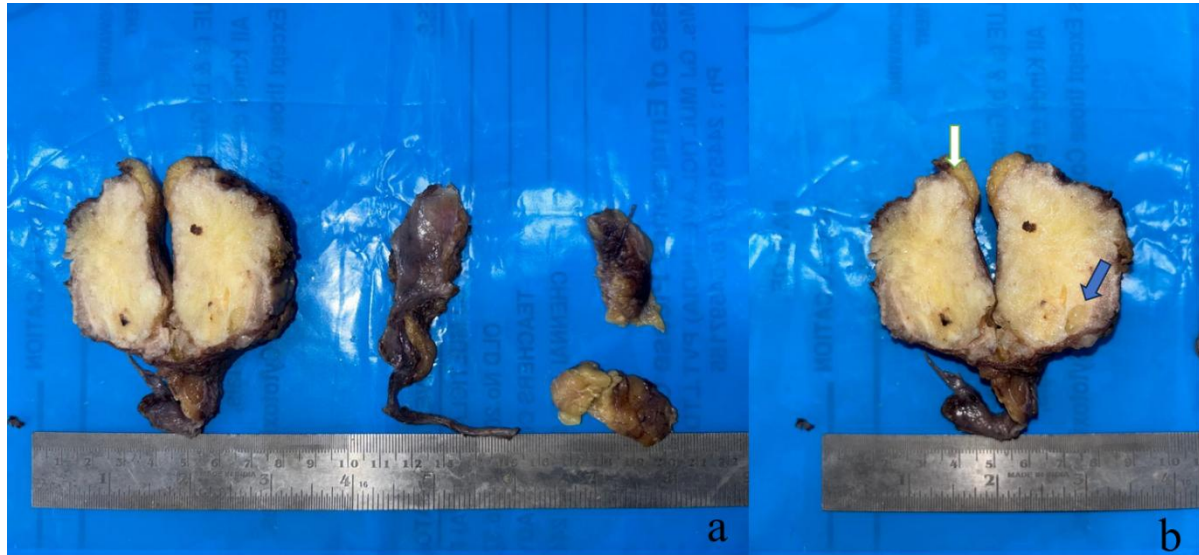
[Table/Fig-1]: Axial CT image showing a well-defined, heterogeneously enhancing exophytic lesion seen arising from the anterior wall of urinary bladder adjacent to superior aspect, measuring $\sim 4.4 \times 3.5 \times 3.3$ cm (Blue arrow)

Transurethral resection of bladder tumor (TURBT) was done and was sent for histopathological examination which revealed hyperplastic urothelial lining with underlying tumor cells predominantly in glandular pattern composed of closely packed glands with intestinal differentiation, goblet cells. Glands are lined by round to polygonal cells with enlarged hyperchromatic nuclei, irregular nuclear membranes, prominent nucleoli, marked anisonucleosis, marked pleomorphism, scant to moderate cytoplasm. The glands shows loss of polarity with marked nuclear crowding. Atypical mitotic figures 15-18/10HPF seen. Background shows desmoplastic stroma with inflammatory infiltrates composed of lymphocytes, plasma cells, neutrophils with foci of mucin pools. The diagnosis was given as feature suggestive of adenocarcinoma (Enteric subtype) [Table/Fig-2 a,b].



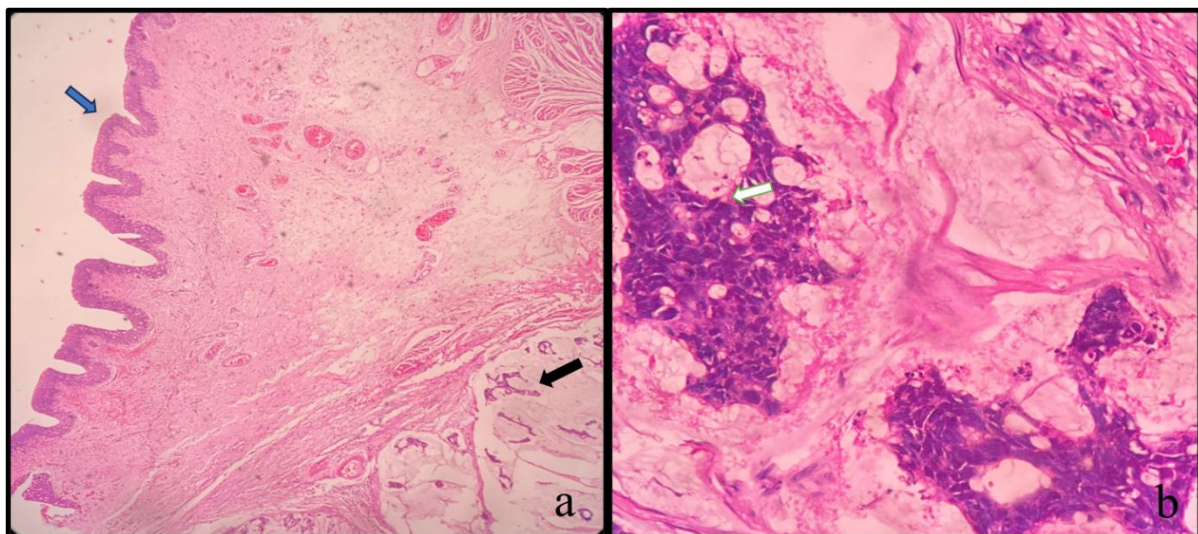
[Table/Fig-2 a,b]: Histopathological images of TURBT specimen a) Hyperplastic urothelial epithelium with underlying stroma shows a glandular lesion (H&E 40x); b) Glands are lined by tumor cells with atypical mitotic figures seen (white arrow) (H&E 400x).

Following which the patient was subjected for partial cystectomy and specimen was sent for histopathological examination. Gross examination revealed a resected specimen of dome of the bladder with a growth in total measuring 6.5x4.5x3.5cm. Inner surface shows an ulcero -proliferative growth measuring 3.8x3.5x3.5cm in the centre. Cut surface of the growth is solid, homogenous, grey white and glistening with focal myxoid areas. A thin strip like fibrofatty tissue measuring 4x1.5x0.3cm and is grey white is noted. Also received in same container two grey yellow fatty tissues of size ranging from 4x2.5x1.5cm to 10x2.5x1cm. [Table/Fig-3 a,b].



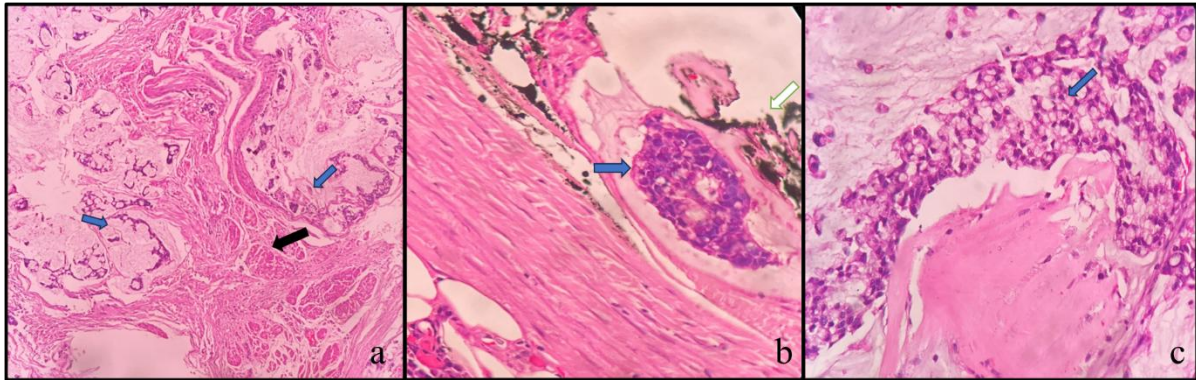
[Table/Fig-3]: Gross features of bladder mass: a) Dome of bladder with a thin strip of fibrofatty tissue and fatty tissue; b) Cut surface of the mass is solid, homogenous, grey white and glistening with focal myxoid areas (blue arrow) and appears to reach upto the vesicular fat margin (white arrow)

Histopathological examination shows hyperplastic urothelial lining with underlying small islands and nests of malignant cells floating in pools and lakes of extracellular mucin separated by fibrocollagenous, irregular, incomplete septae. Cells are small, relatively monomorphic with hyperchromatic round nuclei, coarse chromatin and scant cytoplasm [Table/Fig-4]. Tumor is seen infiltrating into the underlying muscular layer, reaching the vesicular fat margin. Occasional signet ring cell morphology noted [Table/Fig-5]. Adjacent residual urothelium shows hyperplastic reactive changes. Mitosis is 5-6/10 HPF. Lymphovascular invasion and perineural invasion not identified. Section studied from thin strip of fibrofatty tissue and the other two grey yellow fatty tissue shows only sheets of mature adipocytes and is free of tumor [Table/Fig-6].



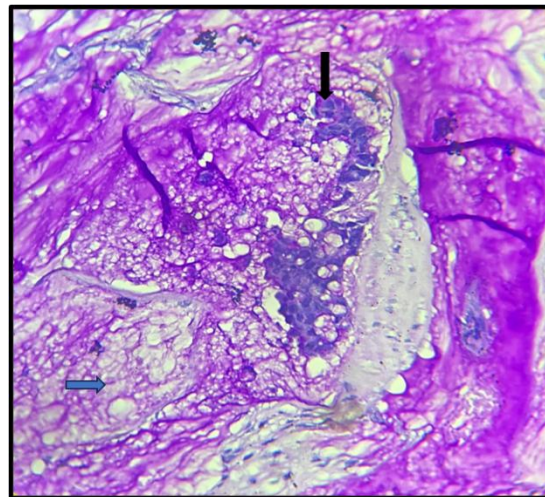
[Table/Fig 4]: Partial cystectomy histopathological images a) Hyperplastic urothelial lining (blue arrow) with underlying small islands and nests of malignant cells floating in pools and lakes of extracellular mucin (black

arrow) (H&E 40x) b) Tumor cells are small, relatively monomorphic with hyperchromatic round nuclei, coarse chromatin and scant cytoplasm.



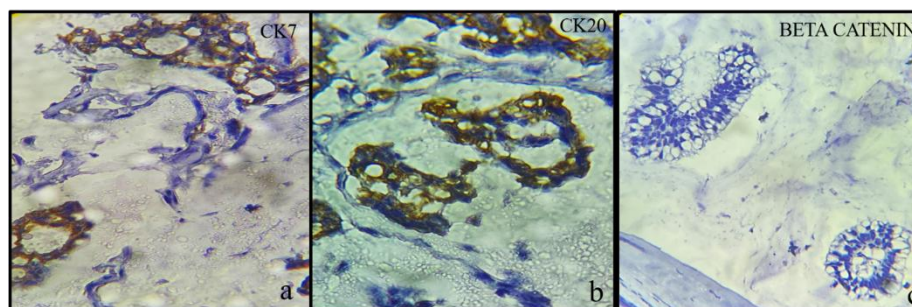
[Table/Fig 5]: a) Tumor (Blue arrows) is seen infiltrating into the underlying muscular layer (Black arrow) (H&E 100x); b) Vesicular fat margin indicated with ink (white arrow) with clusters of tumor cells (blue arrow); (c) Occasional signet ring cell morphology noted (Blue arrow) (H&E 40x).

Special stain with PAS was performed which showed positivity for both intra and extracellular mucin deposits [Table/Fig 6].



[Table/Fig 6]: PAS stain highlighting intracellular (Black arrow) and extracellular mucin (Blue arrow) deposits in magenta colour.

Immunohistochemistry was performed with Cytokeratins (CK) 7 and 20, both of which are positive. In contrast, colonic adenocarcinoma expresses cytokeratin 20 but not cytokeratin 7. Beta catenin was performed to rule out metastasis from primary colon adenocarcinoma. [Table/Fig 7].



[Table/Fig 7]: Immunohistochemical studies a) CK7 showing cytoplasmic and membranous positivity in tumor cells (CK7 stain 400x); b) CK20 showing membranous positivity in tumor cells (CK20 stain 400x); c) Beta catenin negative in tumor cells (Beta catenin stain 400x).

Based on the aforementioned histopathological and IHC findings, the diagnosis of Bladder adenocarcinoma – mucinous type was confirmed. Post-operatively oncologist opinion was sought and was advised 4 cycles of adjuvant chemotherapy. Patient is on regular follow-up till date without any symptoms.

2. DISCUSSION

According to the Globocan cancer observatory data 2022, India is ranked 17th in incidence of new cases and 19th in mortality related to bladder carcinoma, whereas it is ranked 9th in incidence and 13th in mortality worldwide [1]. Bladder cancer is uncommon in individuals younger than 40 years old, and mucinous adenocarcinoma represents an especially rare subtype, accounting for less than 2% of all bladder cancer cases [2]. It usually arises from the bladder dome, trigone, lateral wall and is seen more frequently in regions where schistosomiasis is prevalent and in patients with bladder exstrophy [3]. It primarily occurs in adults, with the highest frequency observed in individuals in their seventies. Adenocarcinoma of the urinary tract is more common in males, with a ~2–3:1 male-to-female ratio. It has various histologic variants that include Enteric adenocarcinoma, Mucinous adenocarcinoma, Mixed adenocarcinoma, Signet-ring cell adenocarcinoma, Adenocarcinoma in situ [4]. Primary mucinous bladder cancer rarely has clinical symptoms. The most prevalent symptoms are suprapubic discomfort, hematuria, dysuria, and bladder irritation. Some people experience bladder discomfort and urination difficulties [5]. Mucinous adenocarcinoma of the urinary bladder is characterized by the presence of extracellular mucin interspersed with tumor cells. In certain instances, a combination of extracellular and intracellular mucin leads to a signet-ring configuration [6]. Primary bladder cancers are rare and typically develop as a result of the hematogenic spread or proximity of other cancers, such as colorectal, prostate, and gynaecological tract cancers [7]. According to previously published research, the pathophysiology of primary bladder mucinous adenocarcinoma gradually changes from mucinous metaplasia and mucinous adenoma to mucinous adenocarcinoma [8]. Systematic approach plays an important role in diagnosing and ruling out other close differentials. Ultrasound abdomen is usually performed when patient presents with symptoms like hematuria, dysuria and abdominal pain. Ultrasound is limited to displaying tumor morphology and its color Doppler flow imaging (CDFI); however, it is unreliable for assessing nodal involvement and deeply infiltrating disease. Multidetector (64-slice) CT scanning serves as the cornerstone in radiological evaluation, demonstrating a sensitivity of 85% and a specificity of 94% for bladder cancer. The 64-slice multidetector CT demonstrates limited reliability in determining extensive locoregional disease, notwithstanding its high spatial resolution. This limitation arises from interobserver variability and the challenges in differentiating the bladder muscle layer [9]. Bladder adenocarcinomas typically show up cystoscopically as single, nodular tumors that are difficult to differentiate from urothelial neoplasms. Through cystoscopy transurethral resection of bladder tumor [TURBT] can be done and sent for histopathological examination [2].

Because primary mucinous bladder cancer is so uncommon, pathological evaluation is still necessary for diagnosis. Immunohistochemical staining may facilitate the differentiation of primary bladder cancer from metastatic adenocarcinomas originating in other sites, such as the colon or prostate [10]. CK7 and CK20 positivity is seen cytoplasm/membrane of the cells and it indicates epithelial tumors. CK7 shows variable positivity (33.3%) for bladder adenocarcinoma and is usually positive (100%) for CK20. In our case, we observed positivity for both CK7 and CK20. Beta catenin is a nuclear/ cytoplasmic marker and is usually positive in case of metastasis from colonic adenocarcinoma. This rules out the most common cause of metastatic bladder adenocarcinoma arising from colonic adenocarcinoma. Serum Prostate specific antigen level (PSA) is 0.3ng/ml and is within normal limits. In addition to serum PSA level, all radiological investigations showed normal prostate, which rules out primary from prostate. Partial cystectomy or transurethral resection may be appropriate for small, well-defined primary bladder or urachal adenocarcinoma associated with long-term survival. Radical cystectomy is typically preferred to partial cystectomy, especially for non-urachal tumors, due to the potential for undetected local invasion on imaging [11]. In our case, considering the age of the patient and small tumor size partial cystectomy was done. During histopathological examination, it was found that tumor had muscular layer invasion and vesicular fat margin involvement. So patient was advised XELOX (Oxaliplatin with capecitabine) regimen of chemotherapy for 4 cycles and continues to be on regular follow up without any symptoms till date. Due to the tumor's rarity, the optimal treatment for primary mucinous adenocarcinoma of the bladder remains undetermined [12,13]. The prognosis of mucinous PBA is primarily contingent upon the stage at which it is diagnosed and treated. The survival rate for tumors confined to the bladder ranges from 75% to 100%; however, fewer than 30% of patients receive an early diagnosis. Adenocarcinoma cells primarily proliferate by infiltrating the deep muscular layer, and both cystoscopy and B-mode ultrasound may be inadequate for evaluating the extent of this infiltration. Consequently, the majority of patients with bladder mucinous adenocarcinoma are diagnosed at T2 or T3 stage, as observed in our patient [14,15].

3. CONCLUSION

The etiopathogenesis of urothelial tumors in younger age group remains unclear. However, few elements like genetic and environmental causes may play a role in their etiology. Few well known factors like tobacco smoking and specific occupational exposures can contribute to the risk of developing urothelial tumors. Existing literature does not provide much information about the root of bladder cancer in the young adult age group. A patient less than 30 years old, who is a non-smoker, without significant medical history, and no occupational exposure, exhibiting these symptoms highlights the

ambiguous nature of this malignancy, and remain understudied. This begs the question of whether bladder cancer and the emergence of other malignancies are related.

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