

# Clear cell adenocarcinoma of urinary bladder: A case report and review

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**Abstract** Clear cell carcinoma is an uncommon but distinct variant of urinary bladder carcinoma histologically resembling the neoplasm in the female genital tract. The histogenesis of this neoplasm is uncertain. The clinicopathologic and histologic features are suggestive of a mullerian origin in some tumors, while some believe it to be glandular differentiation of urothelium or a unique vesicular adenocarcinoma of non-mullerian origin.<sup>[1]</sup> We present a case of clear cell adenocarcinoma in a 74-year-old woman with review of literature along with its differential diagnosis.

**Key Words:** Clear cell adenocarcinoma, cystectomy, lower urinary tract, urinary bladder

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## INTRODUCTION

Clear cell adenocarcinoma (CCA) of the urinary bladder is a rare malignancy with only 41 cases reported in the English literature to date.<sup>[1]</sup> It usually arises from the female genital tract. Its cytologic and ultrastructural features are similar to those of CCA arising in female genital tract to suggest its mullerian differentiation.<sup>[2]</sup> CCA is sometimes found in the lower urinary tract in women, most commonly involving the urethra, where it may arise in paraurethral ducts or diverticula. In males the possible theory of origin is glandular differentiation of urothelium.<sup>[3]</sup>

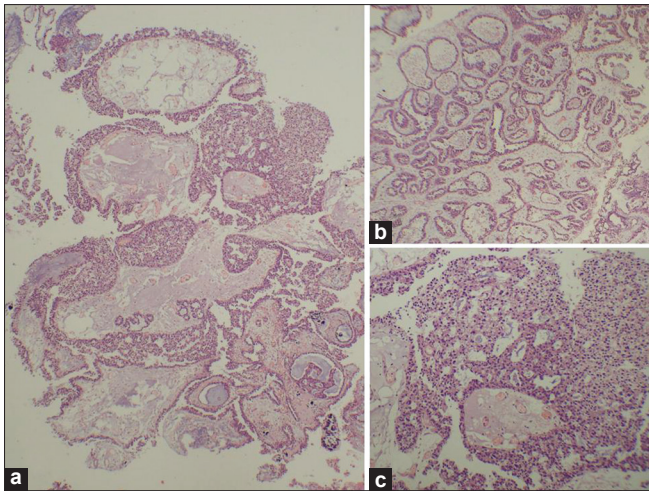
## CASE REPORT

A 74-year-old woman was admitted with complaints of obstructive and irritative lower urinary tract symptoms

for last 2-3 months with a positive history of poor flow, prolonged voiding, thin stream, intermittency, post void dribbling, urgency, urge incontinence and increased frequency. There was no history of hematuria, pyuria, flank pain or any instrumentation. She was diagnosed as hypertensive 10 years ago and was stable on medicines. There was no prior history for any surgery. Clinical examination of patient was fair and systemic examination was normal. On ultrasonography, bladder mass measuring 3.6 cm × 3.2 cm was seen. On cystoscopy, bladder neck was markedly narrowed and occupied by an extensive broad based tumor measuring 4 cm × 3 cm × 2 cm involving both anterior and posterior walls. Bilateral ureteral orifices were normal. Transureteral resection of bladder tumor was done.

The tumor was in multiple fragments, which together measured 5 cm × 4 cm × 0.5 cm. On microscopic examination, the tumor showed a prominent micropapillary, tubulocystic, and glandular pattern [Figure 1]. The papillae were broad and showed extensive myxoid change in the fibrovascular core [Figure 2a]. Many of the cells showed apical snouting [hobnail pattern, Figure 2b]. They had eosinophilic to vacuolated cytoplasm, which stained diffusely with Periodic acid Schiff's stain [PAS, Figure 2c]. Tumor cells showed moderate to marked nuclear atypia and only few mitoses

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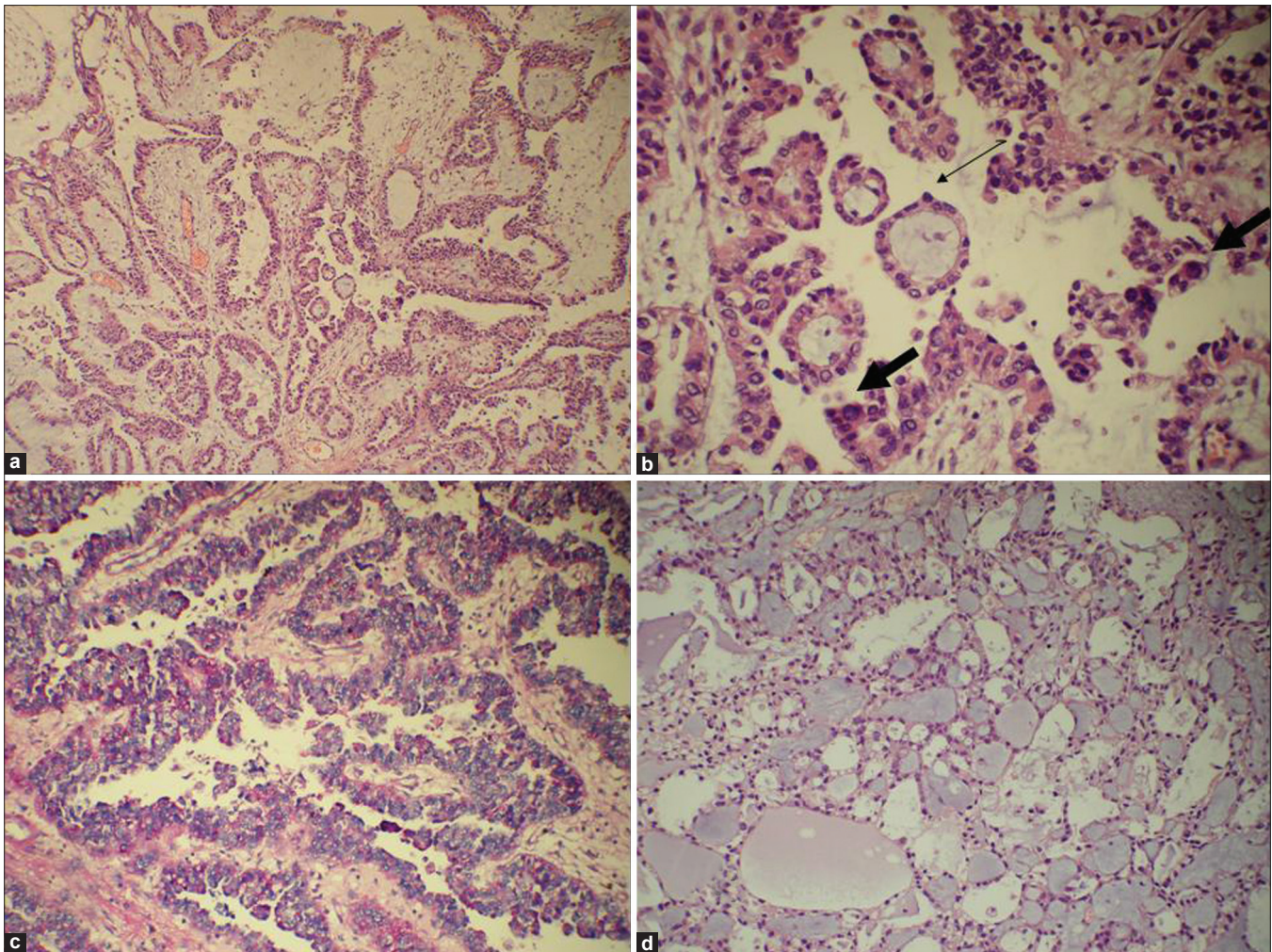
**Figure 1:** Clear cell adenocarcinoma (CCA) urinary bladder with (a) tubulocystic pattern (H and E, x40); (b) tubular pattern (H and E, x100); (c) micropapillary pattern (H and E, x200)

were recognized. Basophilic material was present in lumen of many of the tubules. At places, cribriform pattern was observed [Figure 2d]. Focal infiltration into the muscularis propria was also observed.

On immunohistochemical staining, tumor cells were positive with carcinoembryonic antigen (CEA) [Figure 3a] and focally with CA 125 [Figure 3b] and CK-7 [Figure 3c]. Cells showed strong positivity with p53 [Figure 4a] and Ki-67 [Figure 4b]. Tumor cells did not react with CK-20.

Based on the morphological and immunohistochemical findings, a final diagnosis of clear cell adenocarcinoma of urinary bladder was made.

Patient was given intravesical mitomycin and subsequently radical cystectomy was performed. Examination revealed a



**Figure 2:** Clear cell adenocarcinoma urinary bladder showing (a) broad papillae with myxoid core (H and E, x200); (b) apical snouting (thin arrow) and atypical mitoses (thick arrow) (H and E, x400); (c) PAS positivity in cytoplasm (PAS stain, x400); (d) basophilic material giving cribriform appearance (H and E, x200)

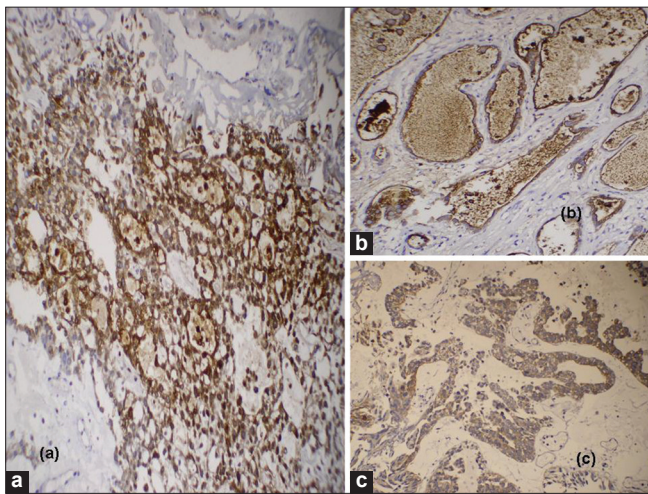


microscopic focus of residual tumor in the bladder neck. However, all the margins were free of tumor. At six months follow-up, patient was reported to be doing well.

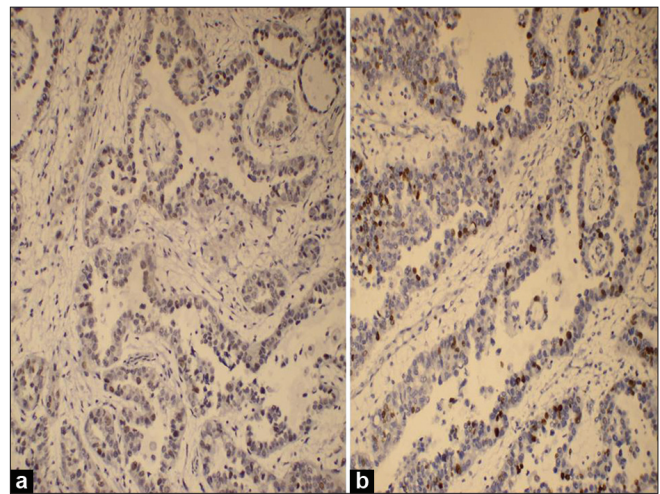
**DISCUSSION**

CCA of urinary tract is rare with only sporadic cases reported in the literature. Till date 41 cases have been reported.<sup>[1]</sup> The histogenesis of CCA in urinary bladder is still unclear. Most information has been gained from single case reports and small case series.<sup>[4]</sup> They were originally categorized as mesonephric adenocarcinoma by Konnak in 1973.<sup>[5]</sup> Later Young and Scully in 1985 introduced the term CCA for these tumors, which

has histologic resemblance to the CCA of female genital tract of mullerian origin.<sup>[6]</sup> CCA of urinary bladder occurs mostly in women, which also supports of a mullerian origin of this tumor. Few authors believed CCA as a morphologic expression of urothelial carcinoma with glandular differentiation.<sup>[3]</sup> In a study conducted by Olivia, nine of thirteen CCA tumors either had minor foci of conventional urothelial carcinoma or foci resembling neoplastic urothelial cells.<sup>[3]</sup> The main differential diagnoses [Table I] of this tumor is nephrogenic adenoma, urothelial carcinoma with clear cell change and metastasis of CCA from ovary and kidney.<sup>[2]</sup> CCA ranges from 1 to 7 cm and most present as polypoidal or papillary masses in trigone region



**Figure 3:** Immunohistochemical stains in clear cell adenocarcinoma urinary bladder (a) cytoplasmic CEA (x400); (b) cytoplasmic CA-125 (x200); (c) cytoplasmic CK-7 (x200)



**Figure 4:** Clear cell adenocarcinoma urinary bladder showing (a) nuclear p53. (x400); (b) nuclear Ki-67 positivity in tumor cells. (x400)

**Table 1: Differential diagnosis of clear cell adenocarcinoma**

		Nephrogenic adenoma	Urothelial carcinoma	Mets from renal cell carcinoma	Mets from CCA ovary	CCA of urinary bladder
Gross		Papillary, polypoidal and sessile structure	Papillary	Solid polypoidal growth	Solid with cystic areas	Papillary and polypoidal
Micro	Pattern	Small tubules and cysts that resemble renal tubules	Papillae with thin cores	Nests with delicate vascular cores	Solid with cystic areas, sometimes papillae formation	Solid, glandular, and tubulocystic
	Hobnail cells	Present	Absent	Absent	Present	Present
	Mitosis	Absent	Variable	Low mitosis	Abnormal mitosis	High mitoses
	Cytoplasm	Scant eosinophilic	Moderate	Abundant and clear	Eosinophilic	Abundant
	Nuclei	Bland	Mild atypia	Bland	Moderate to severe atypia	Moderate to severe atypia
IHC	EMA	+	+	+	+	+
	LMWCK	+	+	+	+	+
	CK 7	+	+	-	+	+
	CK 20	±	+	-	-	±
	CEA	-	+	-	±	+
	Vimentin	-	-	+	-	-
	CA 125	±	±	-	±	+
	AMACR	+				±

CCA - Clear cell adenocarcinoma

of urinary bladder as seen in our case. Glycogen rich clear cells are a hallmark of CCA.<sup>[3]</sup> Solid, papillary, and tubulocystic areas are common and all of these are partially lined by hobnail cells. Cytologic atypia is usually moderate to severe and mitoses are readily apparent.<sup>[2]</sup> In the present case, atypia was marked but mitoses were few. In nephrogenic adenoma-like CCA, usually papillary, polypoidal, or sessile structures are encountered. Microscopically, it is composed of small tubules and cysts lined by a single layer of cuboidal, low columnar, or hobnail cells with scant cytoplasm and bland nuclei.<sup>[2]</sup> Mitotic figures are rare.<sup>[7]</sup> Urothelial carcinoma with clear cell change may resemble CCA, but its architecture is less variable and it lacks hobnail cells.<sup>[8]</sup> Clear cell renal cell carcinoma metastasising to bladder is rare, approximately 20 cases have been reported in literature.<sup>[9]</sup> Histologically, clear cell renal cell carcinoma is architecturally less variable, contains a delicate fibrovascular core, and does not have hobnail cells. Renal cell carcinoma is positive for low molecular weight cytokeratin and vimentin, while CCA is negative for vimentin. Clear cell myelomelanocytic tumor of urinary bladder consists of nests of clear to eosinophilic epithelioid cells with delicate vascular stroma.<sup>[10]</sup> Tumor cells are positive for HMB 45 and smooth muscle actin, while cells in CCA are negative for these markers.<sup>[10]</sup>

## CONCLUSION

CCA is a rare tumor of the urinary bladder with distinctive features. The histogenesis is still controversial. It mostly occurs in women resembling its mullerian counterpart, however, cases reported in men suggest a glandular differentiation (metaplasia) in urothelium/urothelial carcinoma. Unlike urothelial carcinoma, it responds poorly to chemotherapy or

radiotherapy. Radical cystectomy offers best chance of long term survival.

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