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Oncology | Case report

Bladder adenocarcinoma: Role of KRAS mutations in differentiating primary versus metastatic

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ABSTRACT

Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide. Approximately half of patients present with or develop metastatic disease, primarily affecting the liver, lungs, lymph nodes and peritoneum. Involvement of the bladder by colorectal cancer is sufficiently rare to be encountered by an individual surgeon on an infrequent basis. It is challenging to distinguish metastatic colorectal cancer in bladder from primary adenocarcinoma based on histology and immunohistochemistry. However, when matched with molecular analysis such as KRAS mutations and clinico-radiological features, a definitive diagnosis could be reached.

I have a similar case of metastatic colorectal cancer to ureter and urinary bladder which occurred 3 years after the initial diagnosis and treatment. This was an unexpected finding as no radiological features suggestive of urothelial tract involvement was identified. However, based on histology, immunohistochemistry and molecular analysis, a diagnosis of metastatic colorectal cancer was made.

CLINICAL CASE

89-year-old female first presented with abdominal pain and no movement of bowel for 7 days, in July 2020. CT (computed tomographic) scan abdomen and pelvis showed large bowel obstruction due to a circumferential lesion of 50mm in length in the distal sigmoid colon, T3b N1. Bands were noted from tumour to right peritoneal reflection and vaginal vault. Hence, T4a was also probable but no distant metastases were noted.

Colon biopsy was done which showed tubular adenoma with low- and high-grade dysplasia. No invasive malignancy was identified in these superficial biopsies. However, based on radiological findings and discussion at the multidisciplinary meeting, an anterior resection was done. This showed moderately differentiated adenocarcinoma of the rectum with positive circumferential margin on left side and vascular invasion. Tumour invaded the muscularis propria into the perirectal fat. 1/33 lymph nodes showed metastatic carcinoma (pT3 pN1a).

The patient was given post-operative chemoradiotherapy with capecitabine and completed 36 Gray in 20 fractions in December 2020 (of 45 Gray in 25 fractions). However, radiotherapy was discontinued due to profound diarrhoea despite loperamide and discontinuing capecitabine.

CT re-staging scan was done in February 2021 which showed no evidence of disease recurrence.

As a part of colorectal cancer surveillance, CT chest, abdomen and pelvis (CT CAP) was done in June 2023. A left sided grade IV hydronephrosis and a soft tissue density was identified in distal left ureter and left vesicoureteric junction, suggesting underlying transitional cell carcinoma. The right pelvicalyceal system was also prominent and bilateral renal scarring was noted.

A ureteric biopsy was done which showed superficial fragments of possible villous adenoma and invasive malignancy cannot be excluded. Therefore, a repeat second look ureteroscopic biopsy was done after two months. Cystoscopy showed small papillary lesion at 3'o clock of bladder neck. Ureteric orifice and urethra were normal. Rigid ureteroscopy showed a solid and papillary lesion in distal ureter. Bladder and ureter biopsies showed a necrotic glandular lesion arranged as cribriform pattern **(Figure 1)** with focal invasion of the lamina propria. Detrusor muscle was not involved by the tumour. No evidence of carcinoma in situ, intestinal metaplasia or villous adenoma was noted in the background urothelium. The tumour showed strong staining with CK20 and CDX2 **(Figure 2)** and were negative for CK7 and GATA3. The background urothelium showed CK7 and GATA 3 positivity and negative for CDX2 (Figure 2). Beta catenin showed strong membranous and cytoplasmic staining in the tumour.

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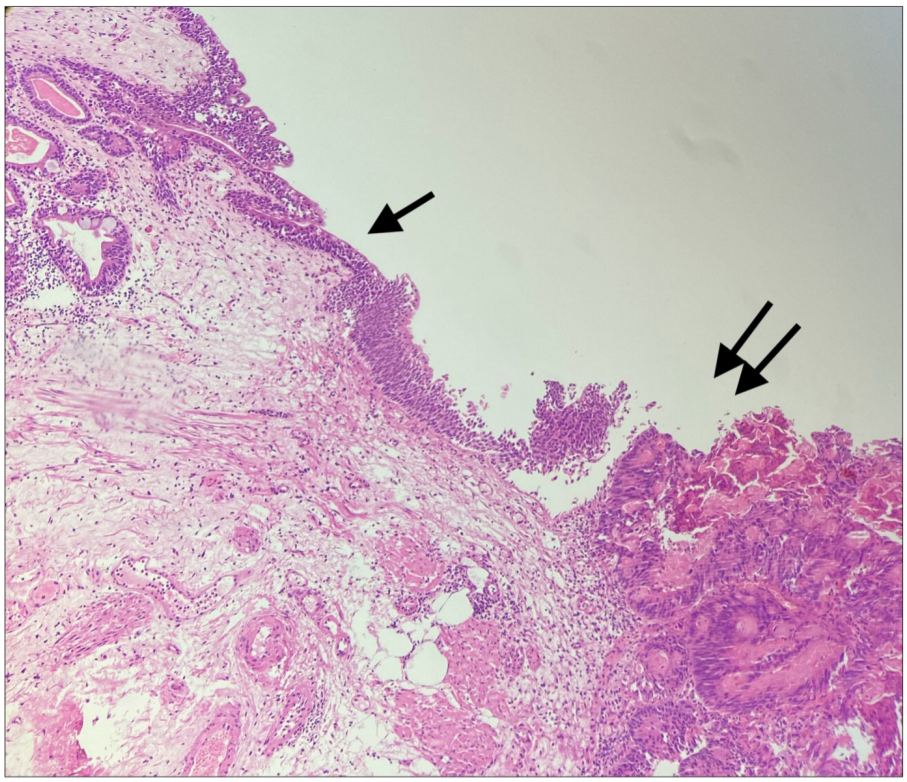

Figure 1: Tumour (⇉) with background normal urothelium (→) (H/E; 4x).

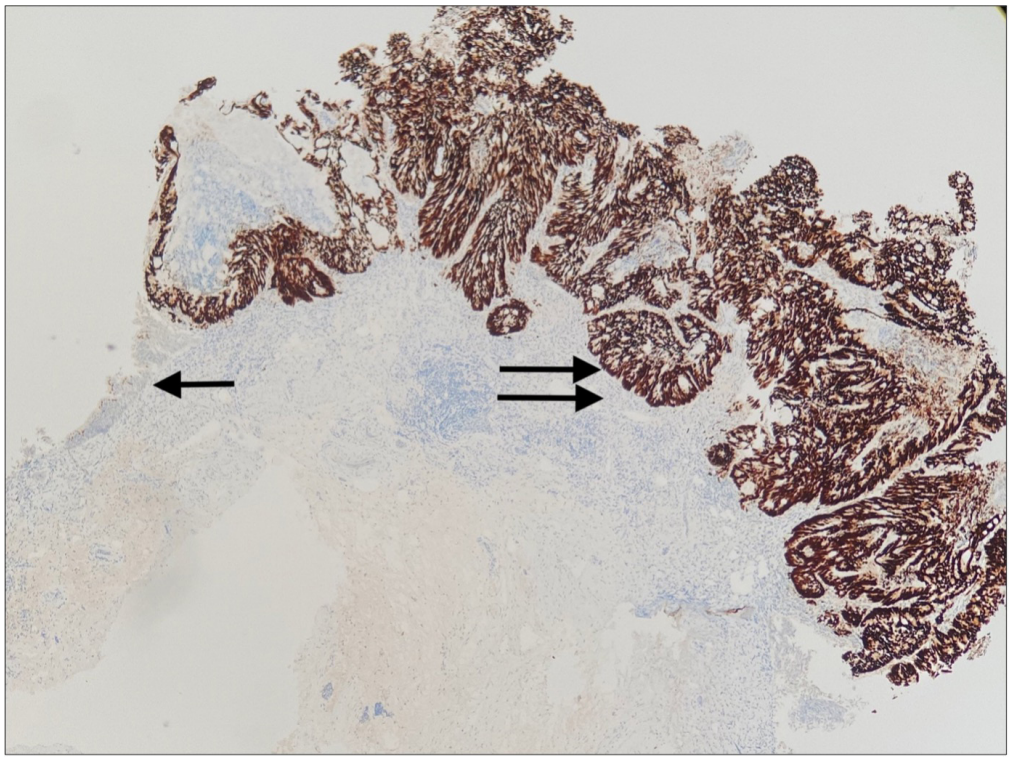

Figure 2: CDX2 staining in tumour cells (⇉) and negative in the background urothelium (→) (4x).

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Overall, a diagnosis of enteric type adenocarcinoma of left ureter and bladder was made. Differential diagnosis included primary bladder adenocarcinoma and metastatic colorectal adenocarcinoma (favoured due to previous history of colorectal cancer).

Further testing included assessment of mismatch repair genes to look for microsatellite instability. Immunostains for mismatch repair genes (PMS2, MLH1, MSH2, MSH6) were normal and no microsatellite instability was detected.

The tissue was then sent for molecular analysis. Mutations for KRAS, NRAS, BRAF and PIK3CA was analysed by PCR amplification and detection. It was found that the tumour showed mutation in KRAS gene in codon 12, variant G12D. No mutation was detected in codons 12, 13, 59, 61, 117 and 146 of NRAS gene or BRAF codon 600 gene.

Hence, a diagnosis of metastatic colorectal cancer to urinary bladder and ureter was made and pelvic radiotherapy was given based on the symptoms of pelvic pain or haematuria. Chemotherapy was not considered due to the underlying side effects in elderly lady.

DISCUSSION

Adenocarcinoma is an unusual form of urinary bladder carcinoma, accounting for 0.5-2% of all primary bladder malignancies [1]. A more common condition is adenocarcinoma originating in an organ adjacent to the bladder, typically the colon, prostate, or female genital organs, with direct invasion into the bladder. The descending colon is a rare site of origin for distant metastases to the bladder.

There is a bit of overlap in immunohistochemical staining between primary adenocarcinoma of bladder and metastatic colorectal carcinoma of bladder. CK7 and CK20 are usually positive, CDX2 is variable and GATA3 is negative in primary bladder adenocarcinoma. Metastatic colorectal carcinomas on the other hand, are positive for CK20 and CDX2 but are negative for CK7 and GATA3 [2]. Beta catenin show strong cytoplasmic and membranous staining in 100% colorectal cancer and nuclear staining in 58% [3] while primary adenocarcinoma only show membranous staining [4]. In the present case as well, the tumour was positive for CK20, CDX2 and negative for CK7 and GATA3. Beta catenin showed membranous and cytoplasmic staining pattern. Also, no evidence of intestinal metaplasia or villous adenoma was seen in the background. Thus, favouring metastatic colorectal carcinoma to bladder.

Defective DNA mismatch repair (MMR) occurs in approximately 15% of sporadic colorectal cancers (CRCs) [5].

It is also seen both dMMR (mismatch repair deficiency) and MSI-H (microsatellite instability-high) occur more frequently in UTUC (upper urothelial tract cancer) than in BC (bladder cancer) [6].

In the present case, immunohistochemistry for mismatch repair genes (MMR) were normal and no microsatellite instability was detected. The sample was therefore sent for molecular analysis to look for KRAS mutation.

KRAS mutations are detected in 93.2% of colorectal cancer patients, with *KRAS* G12D being the most common subtype (30.1%) [7].

With regards to bladder tumours, a mutation in KRAS was found in three (11.5%) of 26 primary bladder adenocarcinomas. Two of these three cases exhibited a G13D mutation, whereas the remaining case contained a mutation in G12V. None of the ten cases of urothelial carcinoma with glandular differentiation displayed KRAS mutation [8].

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CONCLUSION

Present case showed KRAS mutation in codon 12 (G12D) in bladder biopsy, in contrast to G13D mutation seen in primary bladder adenocarcinoma (as stated above). Also, the patient had a history of left sided colorectal cancer with symptoms of haematuria, indicating bladder involvement. Moreover, the background urothelium was normal and no intestinal metaplasia was seen. Hence, further confirming the diagnosis of metastatic colorectal cancer in bladder.

In summary, this is a rare and interesting case to see how molecular analysis helped in the differential diagnosis of bladder adenocarcinoma.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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None

REFERENCES

1. Thomas DG, Ward AM, Williams JL. A study of 52 cases of adenocarcinoma of the bladder. BrJUrol1971; 43:4-15

2. Zuo C, Ye H. Adenocarcinoma. PathologyOutlines.com website. http://www.pathologyoutlines.com/topic/bladderadeno.html. Accessed June 18th, 2024.

3. Elzagheid A, Buhmeida A, Korkeila E, Collan Y, Syrjanen K, Pyrhonen S. Nuclear beta-catenin expression as a prognostic factor in advanced colorectal carcinoma. World J Gastroenterol. 2008 Jun 28;14(24): 3866-71. doi: 10.3748/wjg.14.3866. PMID: 18609711; PMCID: PMC2721444.

4. Amin MB, Trpkov K, Lopez-Beltran A, Grignon D; Members of the ISUP Immunohistochemistry in Diagnostic Urologic Pathology Group. Best practices recommendations in the application of immunohistochemistry in the bladder lesions: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol. 2014 Aug;38(8):e20-34. doi: 10.1097/PAS.0000000000000240. PMID: 25029121.

5. Sinicrope FA. DNA mismatch repair and adjuvant chemotherapy in sporadic colon cancer. Nat Rev Clin Oncol. 2010 Mar;7(3):174-7. doi: 10.1038/nrclinonc.2009.235. PMID: 20190798; PMCID: PMC3767984.

6. Chandran EBA, Iannantuono GM, Atiq SO, et al. Mismatch repair deficiency and microsatellite instability in urothelial carcinoma: a systematic review and meta- analysis. BMJ Oncology 2024;3:e000335. doi:10.1136/ bmjonc-2024-000335

7. Koulouridi A, Karagianni M, Messaritakis I, Sfakianaki M, Voutsina A, Trypaki M, Bachlitzanaki M, Koustas E, Karamouzis MV, Ntavatzikos A, Koumarianou A, Androulakis N, Mavroudis D, Tzardi M, Souglakos J. Prognostic Value of *KRAS* Mutations in Colorectal Cancer Patients. Cancers (Basel). 2022 Jul 7;14(14):3320. doi: 10.3390/cancers14143320. PMID: 35884381; PMCID: PMC9313302.

8. Alexander RE, Lopez-Beltran A, Montironi R, MacLennan GT, Post KM, Bilbo SA, Jones TD, Huang W, Rao Q, Sen JD, Meehan K, Cornwell A, Miravalle L, Cheng L. KRAS mutation is present in a small subset of primary urinary bladder adenocarcinomas. Histopathology. 2012 Dec;61(6):1036-42. doi: 10.1111/j.1365-2559.2012.04309.x. Epub 2012 Jul 17. PMID: 22804747.

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