

CASE REPORT

Advanced primary nonurachal adenocarcinoma of urinary bladder responding to modified FOLFOX6 and capecitabine: a case report

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Abstract

Careful morphology and immunohistochemistry study can make an accurate differential diagnosis of primary adenocarcinoma of urinary bladder from metastatic lesions involving bladder, especially cancer arising in colon, but there is yet no consensus regarding the standard chemotherapy for advanced adenocarcinoma of urinary bladder among medical oncologists. Sustained response to modified FOLFOX6 (fluorouracil, oxaliplatin plus leucovorin) regimen and oral capecitabine for multiple metastases in a patient with primary nonurachal adenocarcinoma of urinary bladder is presented here as a strong support that the frontline chemotherapy for this infrequent malignant disease is just like what could be chosen for colorectal cancer.

INTRODUCTION

Primary adenocarcinoma of urinary bladder is an uncommon tumour which can be further classified into urachal and non-urachal ones. Histologically, they can be subclassified into five common pathologic patterns, including enteric (colonic or intestinal), mucinous, signet-ring cell, not otherwise specified, and mixed types [1]. Distinction from secondary adenocarcinoma involving bladder is difficult but important in diagnosis and management, especially for nonurachal adenocarcinoma which tends to arise from trigone and posterior bladder wall, in contrast to the rather specific location of urachal carcinoma on the dome and anterior wall. The prognosis and survival are poorer in nonurachal than urachal adenocarcinoma [2]. Choosing an adequate chemotherapy regimen for metastatic adenocarcinoma of urinary bladder has long been a dilemma due to its rarity

and lack of clinical trial evidence. We like to present our successful experience of treating multiple metastases from a primary nonurachal adenocarcinoma of urinary bladder with modified FOLFOX6 protocol (fluorouracil, oxaliplatin plus leucovorin) and oral capecitabine, the regimens frequently adopted in frontline chemotherapy for colorectal cancer.

CASE REPORT

A 72-year-old man visited our urology clinic with the chief complaints of urinary hesitancy for 4 months and gross haematuria for 4 days in March 2017. There were also mild pain and tenderness over his back. He was scheduled to receive a transurethral surgical procedure aiming at relieving symptoms of the presumed benign prostate hyperplasia. Surprisingly, a

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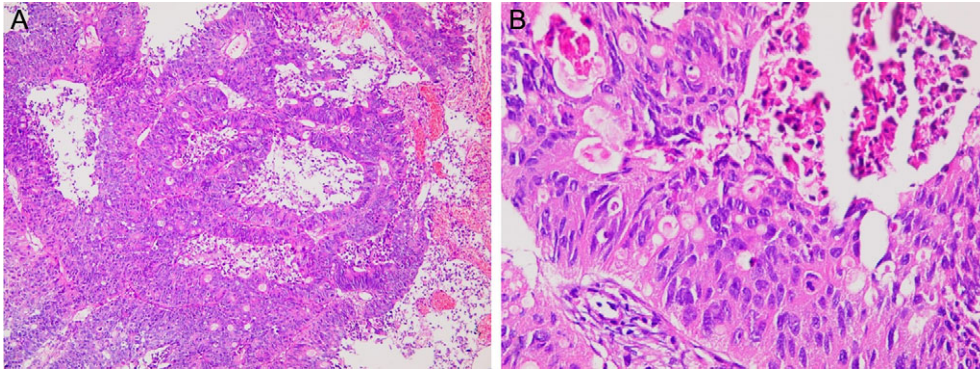


Figure 1: Enteric-type adenocarcinoma arising from urinary bladder (haematoxylin and eosin stain). (A) Cribriform and fused glandular pattern ($\times 100$). (B) Tumour cells similar to colon cancer with coagulative necrosis in the right upper field ($\times 400$).

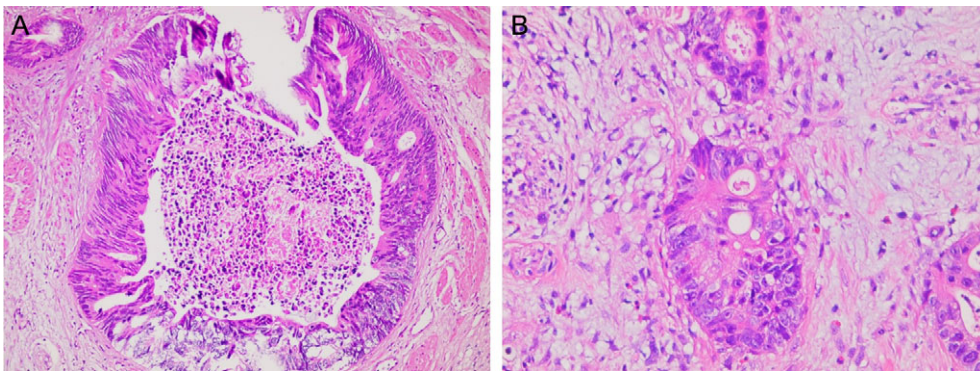


Figure 2: Enteric-type adenocarcinoma invading into prostate gland (haematoxylin and eosin stain). (A) Enteric-type adenocarcinoma with dirty coagulative necrosis ($\times 200$). (B) Enteric-type adenocarcinoma similar to that seen in bladder specimen ($\times 400$).

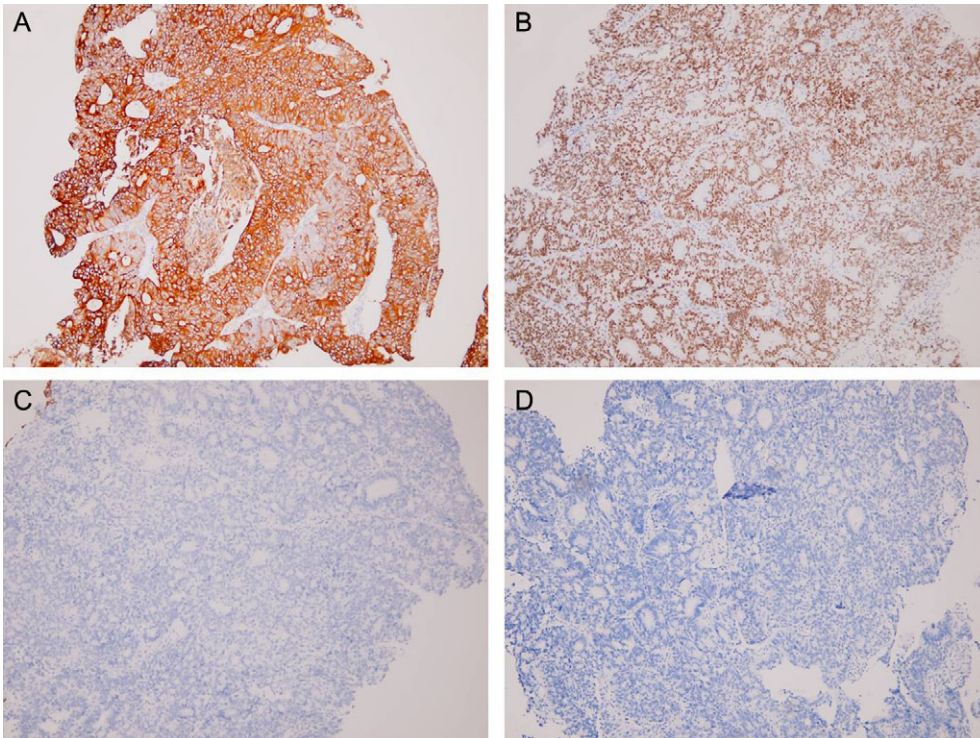


Figure 3: Enteric-type adenocarcinoma arising from urinary bladder. Immunohistochemical staining: Positive for CK20 (A) and CDX2 (B). Negative for CK7 (C) and PSA (D).

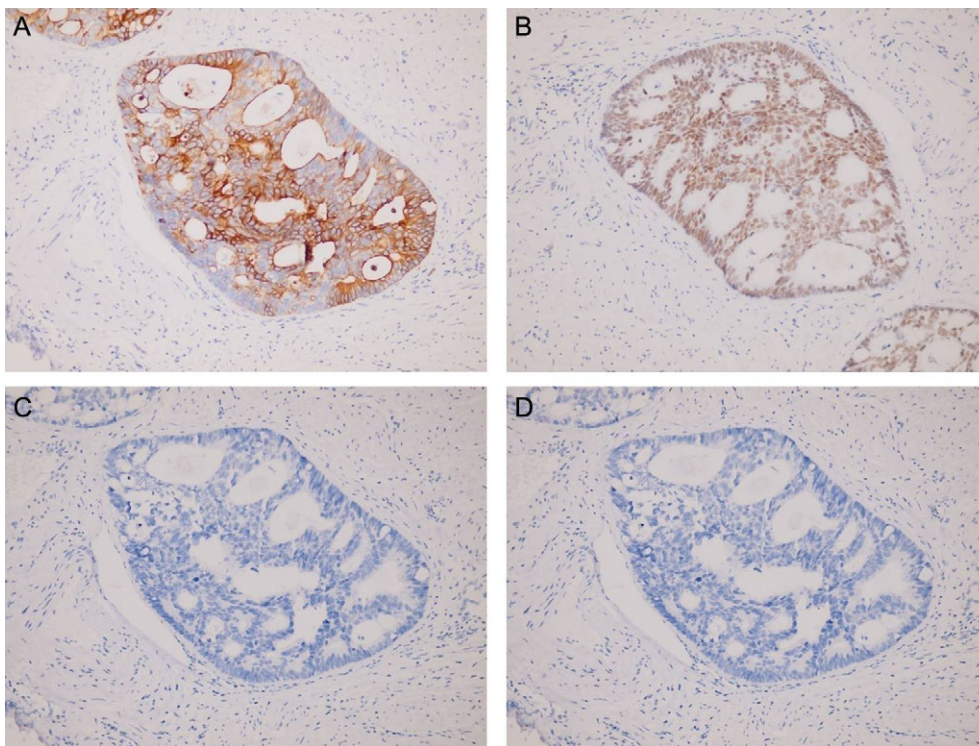


Figure 4: Enteric-type adenocarcinoma invading into prostate gland. Immunohistochemical staining: Positive for CK20 (A) and CDX2 (B). Negative for CK7 (C) and PSA (D).

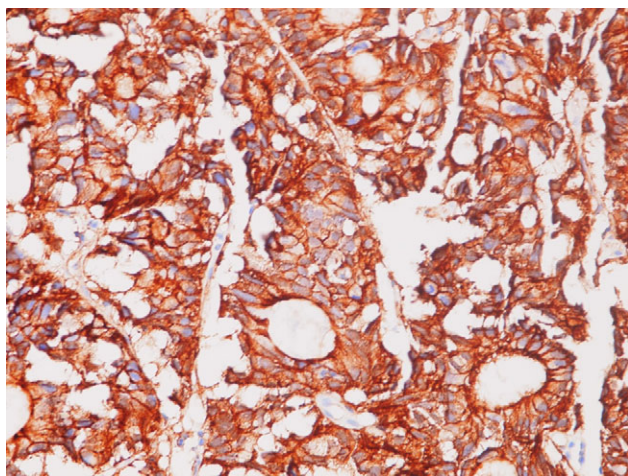


Figure 5: Enteric-type adenocarcinoma arising from urinary bladder. Immunohistochemical staining: Positive for β -catenin over cell membrane and cytoplasm ($\times 400$).

papillary tumour growing over right half of trigone and left bladder neck base with prostate invasion was detected. The tumour was then excised as much as possible for pathologic study.

Specimens from both bladder and prostate turned out to be adenocarcinoma morphologically very similar to that arising from colon (Figs 1 and 2). Immunohistochemical staining revealed that the tumour was positive for cytokeratin 20 (CK20) and Caudal Type Homeobox 2 (CDX2), negative for cytokeratin 7 (CK7) and prostate specific antigen (PSA) (Figs 3 and 4). In addition, β -catenin was strongly reactive over membranous and cytoplasmic portions of the carcinoma cells (Fig. 5). Accordingly, the diagnosis was

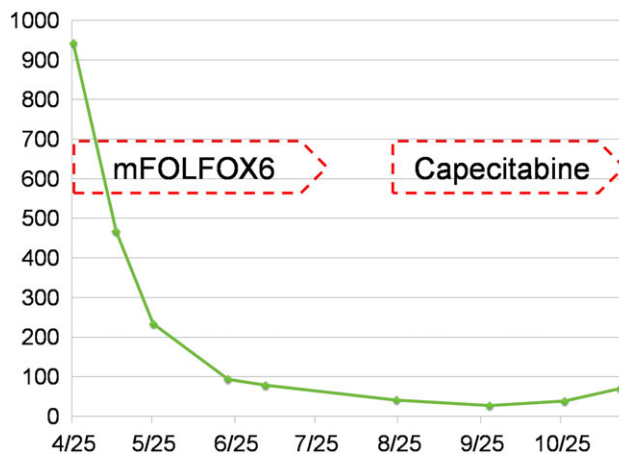


Figure 6: Change of serum tumour marker CA19-9 along the clinical course. Vertical axis: CA19-9 (U/ml). Horizontal axis: date in 2017. Dashed arrow boxes: periods of therapy with mFOLFOX6 and capecitabine, respectively.

consistent with a primary nonurachal adenocarcinoma of urinary bladder with invasion into prostate based on previously published pathologic studies [3]. A colonoscopy failed to detect suspicious malignant lesions except for a hamatomatous polyp in the sigmoid colon.

Bone scan and positron emission tomography (PET)/computerized tomography (CT) scan afterwards showed multiple metastases involving the third and fourth thoracic vertebral bodies, lung, liver and right side adrenal gland besides lymphadenopathy over bilateral neck, left axilla and paraoesophageal regions.

Local radiotherapy with a total dose of 3600 cGy divided in 12 fractions was given over his spinal metastatic sites as the first step

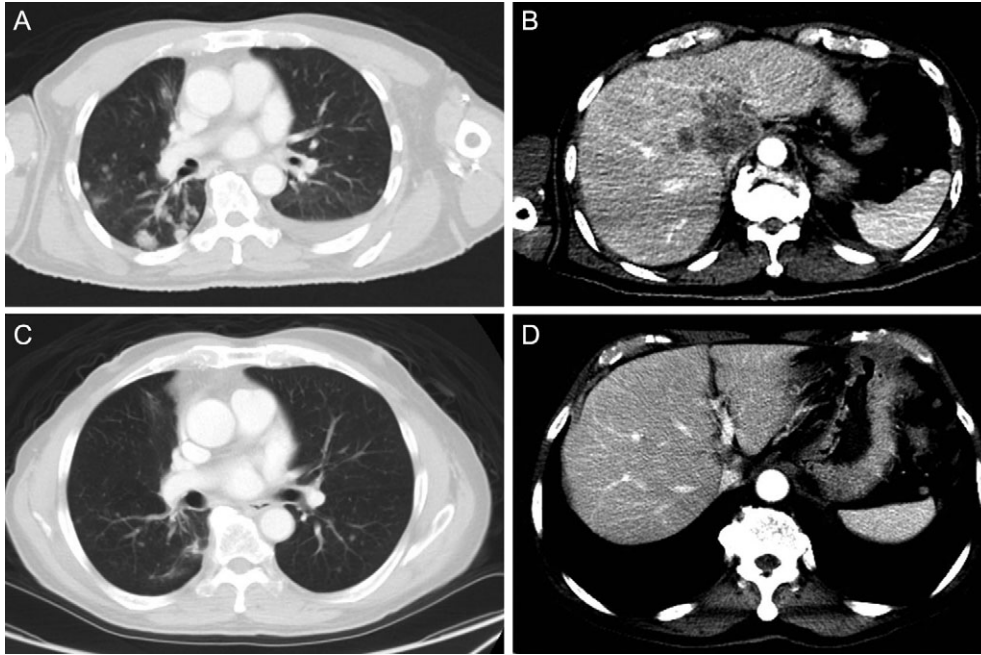


Figure 7: CT scan, lung and liver windows. (A) and (B) 29 March 2017. (C) and (D) 22 November 2017. Much improvement of pulmonary and hepatic metastasis is demonstrated.



Figure 8: CT scan. (A) 15 March 2017. (B) 22 November 2017. Much improvement of right side adrenal metastasis is demonstrated.

of therapy for smoothing back pain in April 2017. During the same period, the patient took one course of oral capecitabine plus intravenous oxaliplatin (CapOX) for his systemic disease. In the subsequent three months, the chemotherapy regimen was shifted to a modified FOLFOX6 (mFOLFOX6): a 2-h intravenous injection of oxaliplatin (85 mg/m^2) on Day 1, a 2-h intravenous injection of

leucovorin (400 mg/m^2) on Day 1, an intravenous injection of fluorouracil (400 mg/m^2), and then a 46-h continuous infusion (2400 mg/m^2) on Day 1, repeated every 2 weeks [4]. Unfortunately, extravasation of the chemotherapeutic agent happened during the seventh cycle of mFOLFOX6. Consequently, intravenous chemotherapy was replaced by oral capecitabine, 2 weeks on/1 week off, after recovery of the severe skin reaction in August 2017. The daily dose of capecitabine was initially 1500 mg, later increased to 2000 mg in December 2017.

The patient's back pain responded to chemotherapy quickly with accompanying downhill change of the serum tumour markers. His CEA and CA19-9 levels decreased from 71.9 ng/ml to 942.5 U/ml, respectively, before mFOLFOX6 infusion in April to 9.85 ng/ml and 69.7 U/ml, respectively, upon taking oral capecitabine in November 2017 (Fig. 6). Much improvement of the metastatic lesions in lymph nodes, lung, liver, and right side adrenal gland could also be demonstrated in the follow-up CT scan (Figs 7 and 8).

DISCUSSION

Differential diagnosis of primary from secondary adenocarcinoma involving urinary bladder is sometimes a puzzling issue because of the similarity between primary bladder adenocarcinoma and colorectal cancer in their tumour marker expression, morphology and immunohistochemistry characteristics. Staining of CK20, CK7 and CDX2 is not able to distinguish one from the other. Nevertheless, β -catenin usually shows nuclear reactivity in colon cancer but membranous and cytoplasmic staining in primary bladder adenocarcinoma, thus becomes a very helpful tool in this respect.

The chemotherapeutic options for advanced urachal adenocarcinoma have confused clinicians in the past decade. Cisplatin-based regimens, probably deriving from what used for urothelial carcinoma, were adopted in early years. Fluorouracil and S1 joined the protocol list later. It was only until recently that oxaliplatin or

irinotecan combined with either fluorouracil, bevacizumab or cetuximab were recognized in a few reports to have high efficacy for this rare cancer [5]. Among them, the FOLFOX regimen (fluorouracil, oxaliplatin plus leucovorin), commonly used for metastatic colorectal cancer, appeared as a reasonable frontline choice after the similarity of morphology and pathogenesis between urachal adenocarcinoma and colon cancer were recognized, supported further by sporadic successful therapy experience [6, 7].

As for the nonurachal adenocarcinoma, so far to our knowledge, satisfactory treatment results with FOLOFX had been disclosed only in three case reports in the English literature. The tumour cell types of these three aforementioned patients were enteric-type [8], mucinous [9] and signet-ring cell [10], respectively. We are glad to present here the astonishing effect of mFOLFOX6 and capecitabine for another enteric-type nonurachal adenocarcinoma of urinary bladder. Although it is difficult to do therapeutic clinical trials for cancer of relatively low incidence, this case presentation surely can provide more evidence for making FOLFOX a preferred first choice chemotherapy regimen for advanced primary adenocarcinoma of urinary bladder, especially the nonurachal ones.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

FUNDING

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ETHICAL APPROVAL

No ethical approval required.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

A copy of the written consent is available for review by the Editor-in-Chief of this journal.

GUARANTOR

Dr Frank S. Fan.

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