Original paper

Comprehensive analysis in mucin-producing urothelial-type adenocarcinoma of the prostate: case study with literature review

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It is critical to distinguish the rare neoplasm of mucin-producing urothelial-type adenocarcinoma of the prostate (MPUAP) from either prostate origin or metastatic adenocarcinoma. This is mainly because they have different tumor staging, clinical behavior and treatment plans. In the current study, we try to fulfill the lack of knowledge in this field.

There were totally 24 MPUAP cases including previous reported 23 cases and adding one new MPUAP case in the current study. We performed IHC and 78 genes panel analysis in two cases of ours.

Most of the cases had urinary obstruction symptoms and normal PSA level. Pathological features showed dissection of the stroma by mucin pools and glands lined by pseudostratified columnar mucinous epithelium with varying degrees of cytological atypia. The IHC results showed positive for CK20, CEA, CDX-2, β-catenin, p53, MUC2 and MUC5AC, negative for PSA, AMACR, GATA3, MUC6, AR and NKX3.1 and variable expression for HMWCK and CK7. Genetic analysis revealed concurrent mutations of *FAT1* (c.10001 T>C) and *HNF1A* in both cases.

The similar morphology features of MPUAP and colorectal adenocarcinoma were seen. Membranous staining pattern of β-catenin and genetic mutation of *FAT1* and *HNF1A* are two distinct features in MPUAP.

Key words: adenocarcinoma, mucin, *FAT1*, *HNF1A*, β-catenin.

Introduction

Prostate cancer is the second most common cancer in men and the fourth most common cancer in both sexes combined. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancer diagnosed in men [1]. The vast majority of histological type in prostatic cancers is acinar adenocarcinoma. Histological variants of prostatic carcinoma have been variably defined. However, it can be briefly divided into two groups: the variant of conventional acinar cancer and cancers with distinct histologic pattern, which are unusual for the prostate [2, 3]. In 1996, Tran and Epstain *et al.* are the first group who reported two cases of mucin-producing urothelial-type adenocarcinoma

of the prostate (MPUAP) [4]. MPUAP is an extremely rare neoplasm and only 23 cases have been previously reported in the English literature [5, 6, 7, 8, 9, 10, 11, 12]. According to the previous studies, MPUAP may originate from the prostatic urethra or the proximal prostatic duct. Patients with this rare type of prostate carcinoma presented urinary obstruction symptoms and may have mucusuria and hematuria. The unique features of MPUAP seems to be the negativity for prostate-specific antigen (PSA) elevation and the lack of response to hormone therapy. Microscopically, MPUAP resembles mucinous acinar adenocarcinoma of the prostate, the urinary bladder adenocarcinoma, and the colonic adenocarcinoma. Moreover, the immunophenotype of MPUAP is similar to the urinary bladder adenocarcinoma [5, 6, 7, 8, 9, 10, 11, 12]. It is important to distinguish MPUAP from mucinous acinar adenocarcinoma of the prostate and from metastatic adenocarcinoma of either the urinary bladder or the colon. This is mainly because they have different tumor staging, clinical behavior and treatment plans. Diagnosis of MPUAP is not straight forward and usually has to exclude the urinary bladder and the colonic metastatic adenocarcinoma. Most of the pathologists are unfamiliar with MPUAP and the immunohistochemical (IHC) results sometime are not conclusive. In the current study, we enrolled two cases of MPUAP to have the comprehensive IHC stains and genetic analysis to fulfill the lack of knowledge in this field.

Material and methods

We retrospectively collected MPUAP cases diagnosed in our hospital between 2010 and 2018. There were only two cases found in our hospital and one of the cases was reported previously [10]. Both of the cases were enrolled for further analysis. This study protocol was approved by the institutional review board of Cardinal Tien Hospital.

The paraffin embedded blocks were cut in 5 μm-thick sections to perform HE and IHC stain. IHC stains were performed, using the Ventana Bench Mark XT automated stainer (Ventana, Tucson, AZ, US). The primary antibodies, cytokeratin 7 (CK7), cytokeratin 20 (CK20), high molecular weight cytokeratin (HMWCK), carcinoembryonic antigen (CEA), CDX-2, β-catenin, PSA, α-methylacyl-CoA racemase (AMACR), GATA3, p53, androgen receptor (AR), MUC2, MUC5AC, MUC6 (ready to use, Ventana, Tucson, AZ, USA) and NKX3.1 (1:50, Bio SB, US) were performed.

Genomic DNAs were extracted from paraffin embedded sections and further performed for library preparation based on multiplex PCR amplification using Sentosa SQ OncoKey Select Panel (Vela Genomics, Singapore). There were 78 genes included in the current panel (*AKT1, AKT2, AKT3, ALK, APC, AR, ARAF, ARID1A, BAP1, BRAF, BRCA1, BRCA2, CDH1, CDK4, CDKN2A, CSF1R, CTCF, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FAT1, FBXW7, FGFR1, FGFR2, FGFR3, FOXL2, GATA3, GNA11, GNAS, GNAQ, H3F3A, HIST1H3B, HNF1A, HRAS, IDH1, IDH2, JAK2, KDR, KEAP1, KIT, KMT2C, KMT2D, KRAS, MAP2K1, MAP2K2, MAP3K1, MET, MLH1, MTOR, NF1, NFE2L2, NOTCH1, NRAS, PDGFRA, PIK3CA, PIK3R1, POLE, PTEN, RAC1, RB1, RET, RHOA, ROS1, SF3B1, SMAD4, SMARCB1, SRC, SMO, SRC, STK11, TP53, TSC1, TSC2, U2AF1, VHL*). Next generation sequencing was performed on the Sentosa SQ301 Sequencing Machine. Subsequently, primary analysis (signal processing and base-calling) was performed by the Sentosa SQ Suite software on the raw sequencing data generated by Sentosa SQ301. After primary analysis, the data was transferred to Sentosa SQ Reporter Server for secondary analysis and report generation.

Table I. Mucin-producing urothelial-type adenocarcinoma of the prostate in the literature and current study

Author and reference	Number of Cases	Year
Tran and Epstein [4]	2	1996
Ortiz-Rey *et al*. [5]	1	2004
Curtis *et al*. [6]	2	2005
Adley *et al*. [7]	1	2006
Niu *et al*. [8]	1	2006
Osunkoya and Epstein [9]	15[a]	2007
Chen *et al*. [10]	1	2012
Sebesta *et al*. [11]	1	2014
Kawasaki *et al*. [12]	1	2017
Current study	2[b]	2018

[a] *2 previously reported cases in 1996 and additional 13 new cases*

[b] *1 previously reported case in 2012 and additional one new case*

Results

There were totally 24 MPUAP cases including previous reported 23 cases and adding one new MPUAP case (Table I). The patient age at diagnosis range from 55 to 81 years old (Table II). Most of the cases had urinary obstruction symptoms. Both of our two cases had excluded metastatic adenocarcinoma from the colon or the urinary bladder by negative of all colonoscopy findings, cystoscopy findings, and computed tomography (CT) scan results. PSA levels were also within normal limit in our two cases (0.8 and 1 ng/ml respectively). Both cases were treated by transurethral resection of prostate (TURP) only. Pathological examination showed dissection of the stroma by mucin pools and glands lined by

Table II. Clinical presentations and management in mucin-producing urothelial-type adenocarcinoma of prostate

	Age	UO	HU	MU	HS	BFP	Meta	Expired	PSA	DRE	Imaging	Treatment
Tran and Epstein [4]		2/2	2/2						WNL			Simple prostatectomy Radical prostatectomy
Ortiz-Rey *et al*. [5]	68							1/1	11.8	Abnormal finding	Heterogeneous right lobe	Hormonal block + TURP
Curtis *et al*. [6]	57-89	2/2	2/2			1/2		1/1	0.3-1.17			TURP + radiotherapy radical prostatectomy + Bil pelvic LN dissection
Adley *et al*. [7]	55								10	Abnormal finding		Radical prostatectomy
Niu *et al*. [8]	60	1/1							3		No abnormality	TURP + Radiotherapy
Osunkoya and Epstein [9]	58-98	15/15	2/15	3/15			4/15	8/15	1.5-4.5			Radical prostatectomy 5/15 Radiotherapy 5/15 Cystoprostectomy 2/15 Pelvic exenteration 1/15 TURP 7/15 Chemotherapy 1/15
Chen *et al*. [10]	59	1/1			1/1				1			TURP
Sebesta *et al*. [11]	81	1/1		1/1					0.38			TURP + radiotherapy + chemotherapy
Kawasaki *et al*. [12]	66	1/1						1/1	0.186		Hypodense mass in right lobe	TURP + chemotherapy
New case	63	1/1	1/1						0.8		Hypodense mass in right lobe	TURP

UO – urinary obstruction; HU – hematuria; MU – muscusuria; HS – hematospermia; BFP – bilateral flank pain; Meta – metastasis; PSA – prostate specific antigen (ng/ml); WNL – within normal limit; DRE – digital rectal exam, TURP – transurethral resection of prostate

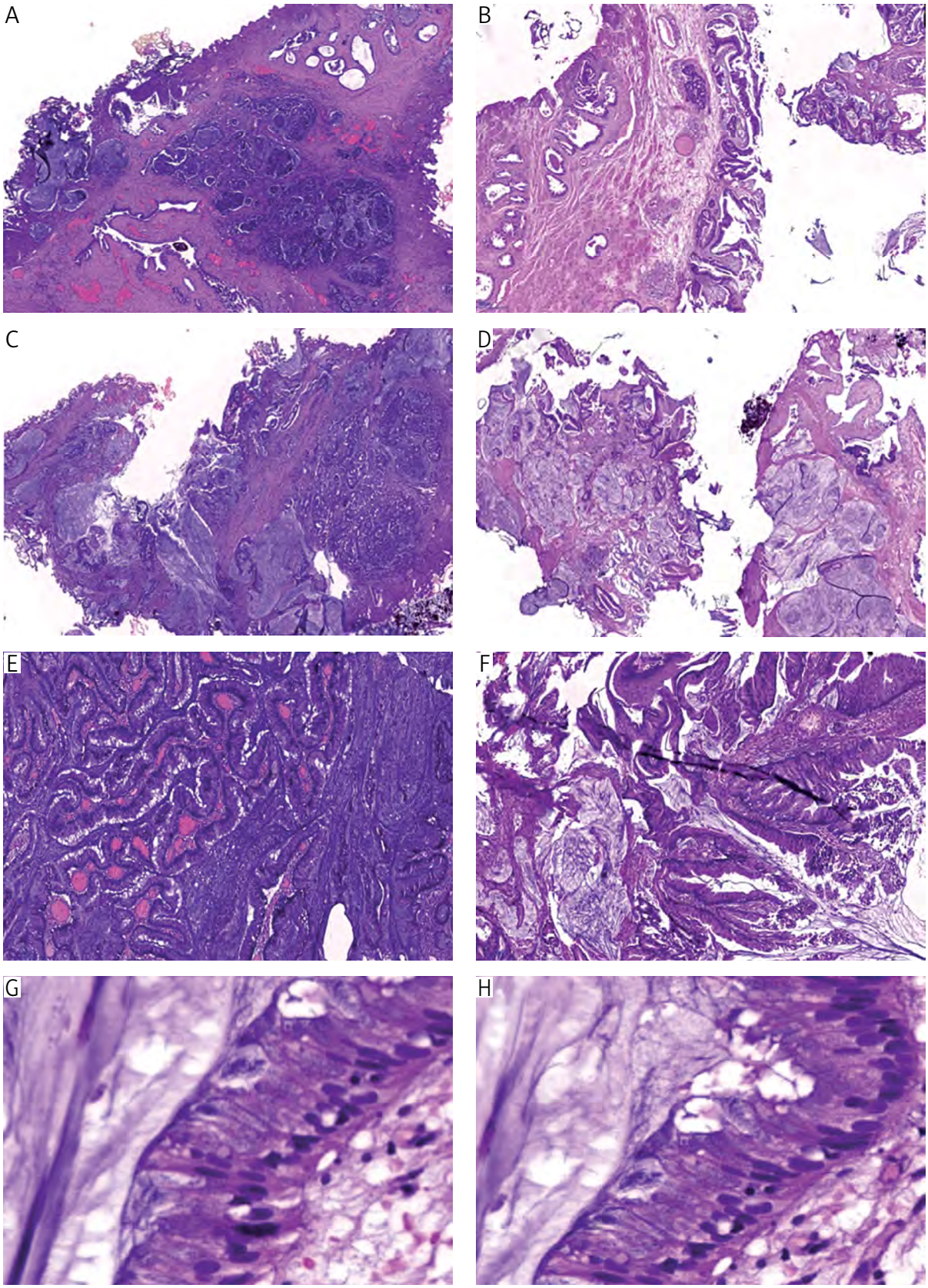


Fig. 1. The morphology of mucin-producing urothelial-type adenocarcinoma of prostate. The picture showed mucin-producing urothelial-type adenocarcinoma of prostate surround by normal prostate glands in both cases (A, B). Mucin pool and dissected stroma was seen in both cases (C, D). Villous features of the adenocarcinoma were also noted (E, F). The neoplastic cells were lined by pseudostratified columnar mucinous epithelium with varying degrees of cytological atypia (G, H). Left panel is the case presented in previous report by Chen *et al*. [10] and right panel is the new case

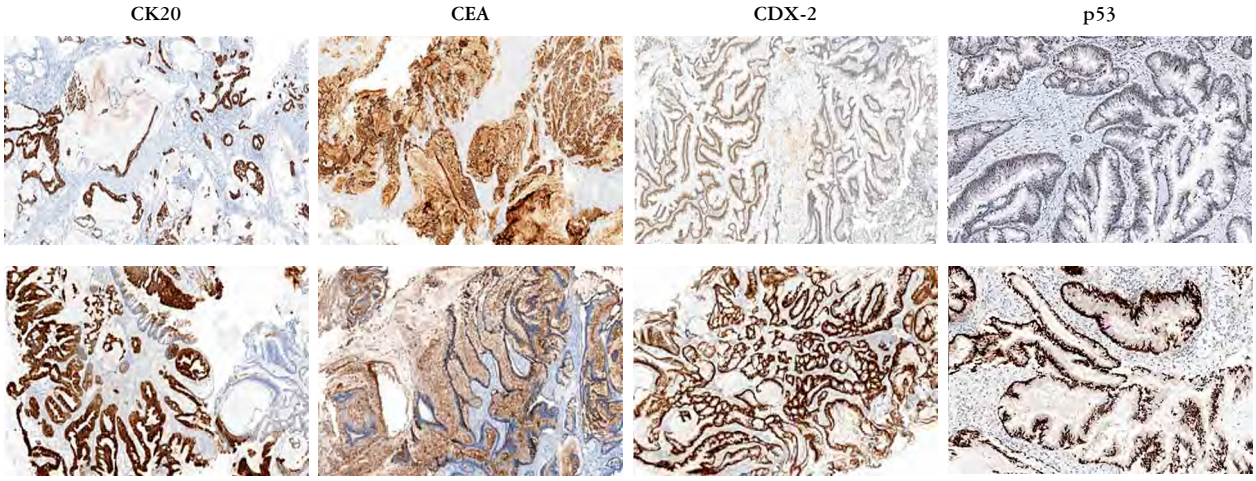
Table III. Immunohistochemical results of mucin-producing urothelial-type adenocarcinoma of the prostate

Author and reference	PSA	PSAP	PSMA	CK20	CEA	CDX2	β-CATENIN	CK7	HMWCK	AMACR	NKX 3.1	GATA3	P53	AR	MUC2	MUC5AC	MUC6
Tran and Epstein [4]	(–)	(–)			(+)												
Ortiz-Rey *et al.* [5]	(–)	(–)		(+)	(+)			(+)	(+)*								
Curtis *et al.* [6]	(–)	(–)		(+)	(+)			(+)	(+)*								
Adley *et al.* [7]	(–)	(–)		(+)	(+)	(+)		(+)	(+)	(–)							
Niu *et al.* [8]	(–)				(+)												
Osunkoya and Epstein [9]	(–)	(–)		(+)		(–)	(–)	(+)	(+)								
Chen *et al.* [10]	(–)		(–)	(+)	(+)	(+)*	(+)†	(+)	(+)	(–)	(–)	(–)	(+)	(–)	(+)	(+)	(–)
Sebesta *et al.* [11]	(–)	(–)		(+)		(–)		(+)				(+)					
Kawasaki *et al.* [12]	(–)		(+)		(+)	(+)*					(+)						
New case	(–)			(+)	(+)	(+)	(+)†	(–)	(–)	(–)	(–)	(–)	(+)	(–)	(+)	(+)	(–)

** Focal staining pattern*

† Membranous staining pattern

PSA – prostate specific antigen; PSAP – prostatic specific acid phosphatase; PSMA – prostate specific membrane antigen; CEA – carcinoembryonic antigen; CK7 – cytokeratin 7; HMWCK – high molecular weight cytokeratin; CK20 – cytokeratin 20; AMACR – α-methylacyl-CoA racemase; AR – androgen receptor



CK20 – cytokeratin 20; CEA – carcinoembryonic antigen

Fig. 2. Immunohistochemical stains of colonic marker and p53 in mucin-producing urothelial-type adenocarcinoma of prostate. The colonic markers of CK20, CEA and CDX-2 were all positive results as well as p53 overexpression. Upper panel is the case presented in previous report by Chen *et al*. [10] and lower panel is the new case

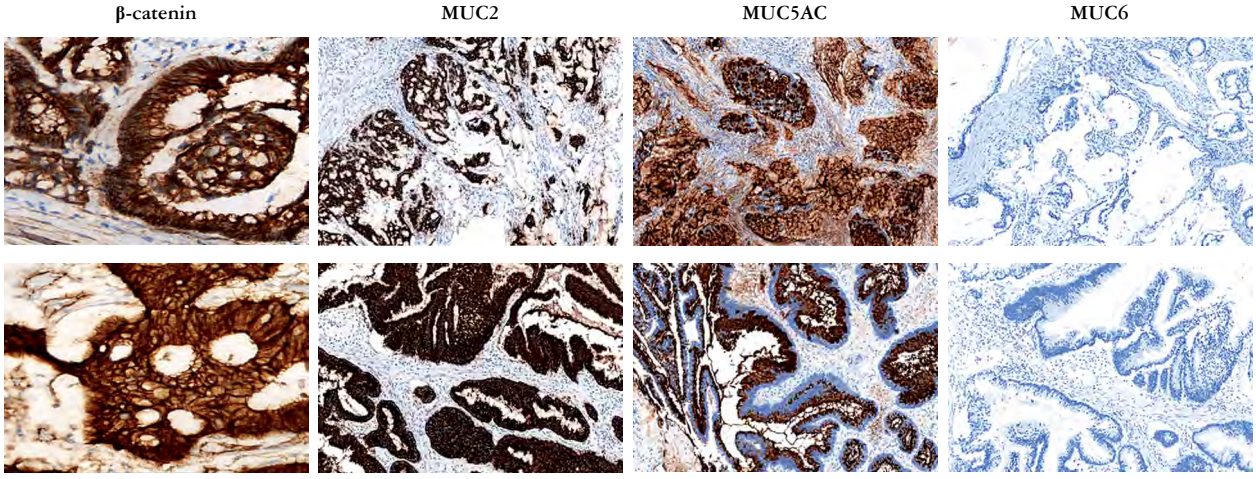


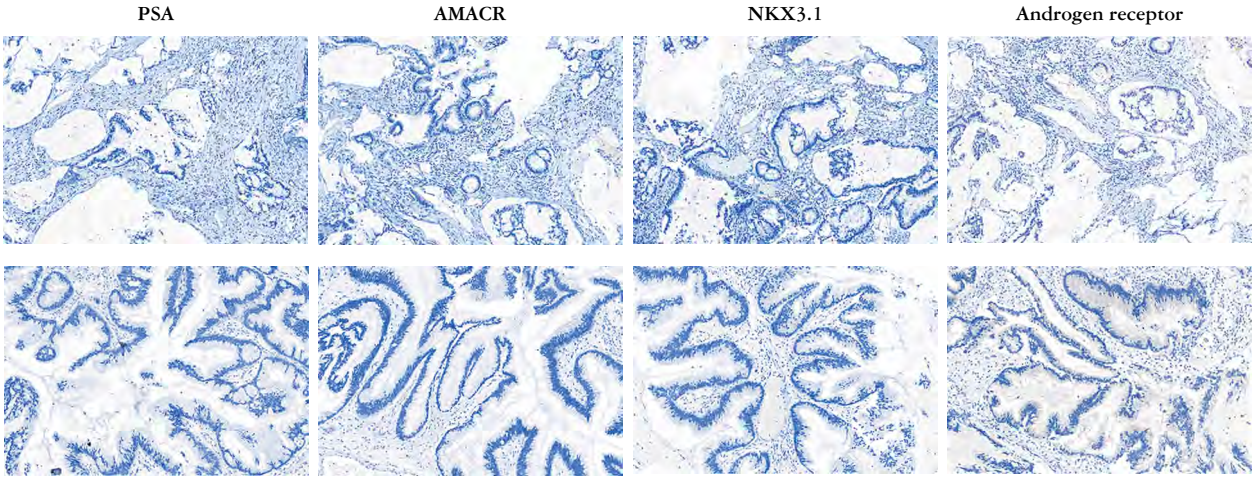
Fig. 3. β-catenin expression and variable MUC staining results in mucin-producing urothelial-type adenocarcinoma of prostate. Strongly immunoreactive for β-catenin and the expression pattern was mainly membranous pattern rather than nuclear pattern in colonic adenocarcinoma. Variable staining results were seen in different MUC stains.
Upper panel is the case presented in previous report by Chen *et al*. [10] and lower panel is the new case

pseudostratified columnar mucinous epithelium with varying degrees of cytological atypia. Villous features were also noted. Glandular metaplasia and *in situ* adenocarcinoma were not identified (Fig. 1). In the Table III, the IHC results showed positive for CK20, CEA, CDX-2 (focal), β-catenin (membranous staining), p53, MUC2 and MUC5AC, negative for PSA, AMACR, GATA3, MUC6, AR and NKX3.1 and variable expression for HMWCK and CK7 (Figs. 2-5). Genetic analysis revealed concurrent mutations of *FAT1* and *HNF1A* in both cases (Table IV). Among all the somatic mutations, *FAT1* mutation locus of c.10001 T>C was presented in both cases. The change of amino acid from proline to alanine was identified (p.V3334A).

Discussion

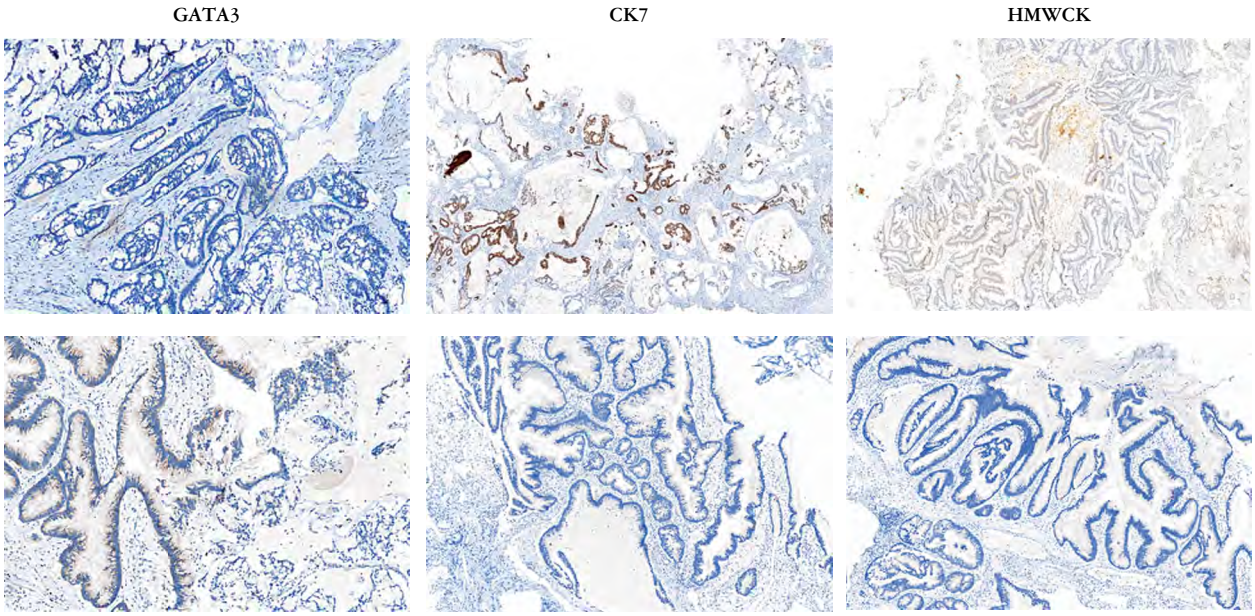
There were only two cases of MPUAP diagnosed in our hospital during the past 9 years (2010-2018). One case was reported previously in 2012 [10]. Another new case was diagnosed in 2014. Both of these two cases had excluded metastatic adenocarcinoma from either the urinary bladder or the colon by colonoscopy findings, cystoscopy findings, and CT scan results. After a 78 genes analysis in MPUAP, we identified concurrent mutations of *FAT1* and *HNF1A* in both cases.

In total of 24 cases including one new enrolled case and other 23 cases in the literature, most of the patients present urinary obstruction symptoms 83%



PSA – prostate specific antigen; AMACR – α-methylacyl-CoA racemase

Fig. 4. Mainly negative expression results of prostatic markers in mucin-producing urothelial-type adenocarcinoma. All negative staining results of PSA, AMACR, NKX 3.1 and androgen receptor. Upper panel is the case presented in previous report by Chen *et al*. [10] and lower panel is the new case



CK7 – cytokeratin 7; HMWCK – high molecular weight cytokeratin

Fig. 5. Other immunostaining results in mucin-producing urothelial-type adenocarcinoma. Negative staining results of GATA3 and variables staining results in CK7 and high molecular weight cytokeratin. Upper panel is the case presented in previous report by Chen *et al*. [10] and lower panel is the new case

(20/24), hematuria 29% (7/24), mucusuria 16% (4/24), bilateral frank pain 4% (1/24), hematospermia 4% (1/24), and disseminated intravascular coagulation 4% (1/24) [5, 6, 7, 8, 9, 10, 11, 12]. The PSA levels were usually not elevated with a mean of 2.27 ng/ml (range 0.2-11.8). Metastatic diseases developed in the end of clinical course and metastasis to the lung in four cases, liver in three cases, pelvic wall in two cases, testis and bone in one case. Transurethral resection or surgical resection was performed in all cases, and hormone therapy was performed in one case, radiation therapy was performed in eight cases and chemotherapy was performed in three cases. Eleven patients died because of the disease with an average overall survival time of 4.3 months [12].

The typical pathological findings are large mucin pool with floating neoplastic cells or glands lined by atypical tall pseudostratified columnar epithelium. Villous feature (9/24), necrosis (3/24), signet ring cells (5/24), perineural and vascular invasions (2/24)

Table IV. Genetic mutation identified in both mucin-producing urothelial-type adenocarcinoma of prostate cases

Case	Gene	cDNA mutation	Amino acid mutation
1*	*FAT1*	c.10001 T>C	p.V3334A
	FAT1	c.4985 A>G	p.N1662S
	HNF1A	c.79 A>C	p.I27L
2	*FAT1*	c.10001 T>C	p.V3334A
	FAT1	c.9998 de1 C	p.P3333fs
	FAT1	c.9932 del G	p.G3311fs
	HNF1A	c.526+1 G>T	

** Published previously by Chen et al. {10}*

were also reported [5, 6, 7, 8, 9, 10, 11, 12]. It is necessary to differentiate MPUAP from either mucinous adenocarcinoma of the prostate or other metastatic adenocarcinoma. Mucinous adenocarcinoma of the prostate reveals mucin, cords of cuboidal epithelium and cribriform glands with bland cytological nuclei. Non-urachal adenocarcinoma of the urinary bladder and adenocarcinoma of the colon are identical in its morphology of MPUAP. The ways to distinguish these two entities are by tumor location and sometimes immunohistochemical features. MPUAP may arise from malignant transformation of the urethritis glandularis involving the urothelial lining of the prostatic urethra or the proximal prostatic ducts [4]. The presence of *in situ* adenocarcinoma in an overlying prostatic urethra suggests that MPUAP arises in the prostatic urethral urothelium. Among the total 24 cases, there were 11 cases with glandular metaplasia or *in situ* adenocarcinoma concurrent near MPUAP [12]. Another rare neoplasm in the prostate is the prostatic ductal adenocarcinoma (PDA). PDA may arise either in large primary periurethral prostatic ducts or in the peripheral prostatic ducts. Ductal adenocarcinomas are composed of tall columnar cells arranged in cribriform, papillary, solid, single glands, and PIN-like patterns [13]. However, it is easier to differentiate MPUAP from PDA mainly by the large amount of mucin pool.

The immunohistochemical profile of MPUAP showed positive for CK7, CK20, HMWCK, CEA and negative for PSA, prostatic specific acid phosphatase (PSAP), AMACR. Moreover, CDX2 and β-catenin expression were variable [12]. This immunohistochemical features also suggested that MPUAP arises in the prostatic urethral urothelium. To compare with PDA, the positive results of CK7, CK20, CEA and CDX2 in PDA were similar to MPUAP. This makes the further evaluation for the possibility of metastatic adenocarcinoma is needed in both MPUAP and PDA [14]. However, the positive staining results of AMACR, PSA, PSAP or prostate specific membrane antigen (PSMA) will distinguish PDA from MPUAP easily [15]. Moreover, AR showed positive results in PDA while it is negative in MPUAP. This negative staining result of AR may partially explain the poor response to the hormone therapy. Kawasaki *et al*. in 2017 found that prostate marker NKX3.1 was seen in the MPUAP tumor cells with nuclear staining pattern [12]. But our two cases did not express NKX 3.1. Similar situation was seen in the GATA3 stain. Sebesta *et al.* in 2014 found that GATA3 was seen in the MPUAP but our two cases did not express GATA3 [11]. This may be due to different antibody clone or it is truly variable in MPUAP (Fig. 5). Another issue worthy of address is that the staining pattern of β-catenin, if present, is primarily membranous rather than nuclei staining (Fig. 3). On the contrary, β-catenin staining pattern in colorectal adenocarcinoma is mainly nuclear pattern [16]. This finding may be a clue for differential diagnosis from colorectal metastatic adenocarcinoma. Other mucin stains including MUC 2 and MUC5AC showed positive results while MUC6 showed negative results in both of MPUAP cases. Still, this finding is based on our two MPUAP cases. More data is mended for further confirmation.

In prostate cancers, lesions in the PI3K pathway occur in approximately 25-70%, genomic deletions and inactivating point mutations of *PTEN* occur in 50% and deletions and point mutations in the *TP53* locus occur in 70% [17, 18, 19]. *MYC* gene is commonly amplified in prostate cancer [17, 18, 20, 21, 22, 23] but *RB1, KRAS, RAF1*, and *BRAF* gene alteration are rarely seen in prostate cancer [21, 22, 23, 24]. There are limited data about the genetic profile of adenocarcinoma of the urinary bladder and the urachus. *KRAS* mutations are described in a subset arising in the urinary bladder and the urachus. Microsatellite instability has also been reported in the urachal adenocarcinoma [25, 26]. Mutations in genes of *FAT1* and *HNF1A* were less reported in adenocarcinoma of prostate and the urinary bladder.

In human cells, protocadherin FAT1 (FAT1) is a protein that in humans is encoded by the gene *FAT1*. It is localized to the cell membrane, often concentrated at filopodia, lamellipodia, and sites of cell-cell contact. FAT1 has been shown to regulate cell-cell association and actin dynamics [27, 28]. *FAT1* is a frequent target of the chromosomal loss events on chromosome 4q35 seen in a wide range of human cancers. Inactivated FAT1 is unable to sequester β-catenin at the cell membrane, and thereby promotes Wnt signaling and tumor growth [27, 29]. An overview of *FAT1* gene mutation and tissue distribution from catalogue of somatic mutations in cancer (COSMIC) database, 8.78% (300/3415) cases were distributed in the large intestine, 1.96% (51/2604) cases were distributed in the prostate and 6.49% (73/1125) cases were distributed in the urinary tract [30]. In COSMIC database,

there were only 5 cases with *FAT1* (c.10001 T>C) mutation identified and all 5 cases were distributed in the prostate [31]. Mutation of *FAT1* (c.10001 T>C) should be a distinct genetic feature in MPUAP because it was identified in both of our cases.

The *HNF1A* gene codes for the hepatocyte nuclear factor 1α (HNF1α) that expressed in organs of endodermal origin. The HNF1 family regulates complex networks of metabolism and organ development [32]. It has been shown to affect intestinal epithelial cell growth and cell lineages differentiation [33, 34, 35]. Significantly lower levels of HNF1α in pancreatic tumors and hepatocellular adenomas than in normal adjacent tissue suggested that HNF1α might play a possible tumor suppressor role [36, 37]. When searching *HNF1A* mutation in the COSMIC database, 6.56% (40/610) cases were distributed in the large intestine, 6.63% (33/498) cases were distributed in the prostate and 1.47% (6/408) cases were distributed in the urinary tract [38]. Moreover, there are only 25 cases with *HNF1A* (c.79 A>C) mutation identified in the COSMIC database. Among these 25 cases, 40% (10/25) cases were distributed in the soft tissue, 36% (9/25) cases were distributed in the liver, 16% (4/25) cases were distributed in the prostate, 4% (1/25) cases in the colon and 4% (1/25) cases in the urinary tract [39]. At last, *HNF1A* (c.526+1 G>A) mutation was identified instead of c.526+1 G>T in COSMIC database. Whether *HNF1A* mutation an innocent bystander or a driver mutation were hard to be determined in the current study. Nevertheless, it may not be a key mutation due to the different *HNF1A* point mutation in our two cases.

MPUAP are extremely rare neoplasms and there were only two cases included in the current study. Although clinical presentations and histological features of both cases were similar to the other reported cases, the IHC features were variable. Both of our cases were NKX 3.1 negative and β-catenin positive with membranous staining pattern. Although *FAT1* and *HNF1A* mutation were identified among the 78 genes analysis, more genetic analysis such as translocation or copy number variation are needed.

In conclusion, the similar morphology features of MPUAP and the colorectal adenocarcinoma were supported by not only immunohistochemical stain results but also genetic mutation found mainly in the colon and the prostate. Membranous staining pattern of β-catenin and genetic mutation of *FAT*1 and *HNF1A* are two distinct features in MPUAP. However, more case study is needed for further confirmation and exploration.

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The authors declare no conflict of interest.

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