Scientific Research Publishing

Journal of Cancer Therapy, 2021, 12, 240-253
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Bladder Malignant Granular Cell Tumor with EP300 Gene Mutation: A Case Report and Literature Review

Di Zhu*, Xinle Ren*, Yi Luo, Bing Huang, Jian Huang#

The Center of Pathological Diagnosis and Research, Affiliated Hospital, Guangdong Medical University, Zhanjiang, China
Email: #18665763598@163.com

How to cite this paper: Zhu, D., Ren, X.L., Luo, Y., Huang, B. and Huang, J. (2021) Bladder Malignant Granular Cell Tumor with EP300 Gene Mutation: A Case Report and Literature Review. *Journal of Cancer Therapy*, **12**, 240-253.
https://doi.org/10.4236/jct.2021.125023

Received: April 25, 2021
Accepted: May 11, 2021
Published: May 14, 2021

Abstract

Background: Malignant granular cell tumor (GCT) is extremely rare. Malignant GCT with EP300 gene mutation in the bladder has not been reported in the literature. **Case Presentation:** We report a special case of 45-year-old female with malignant GCT of the bladder. Pathological examination showed that the mass was 11 × 11 × 4.5 cm in size, involved in the bladder's posterior wall. Under the microscope, the tumor cells were arranged in the shape of a nest or cord to infiltrate the bladder's wall. The tumor cells were pleomorphic, red-stained granular within the cytoplasm, with increased nuclear/cytoplasmic ratio, vacuolar nuclei, and obvious nucleoli. The tumor cells were showed obvious nuclear atypia, and the mitosis was more than 5/50HPF. Coagulative necrosis was widely showed within the tumor. Immunohistochemistry (IHC) showed that S-100, NSE, CD68, CR, α-AT, and TFE-3 were strongly positive, and the Ki-67 proliferation index was around 15%. The next-generation high throughput sequencing indicated that EP300 gene was missense mutated (c.457A > G) with 33% mutation abundance, and genes of DPYD (c.1627A > G), ERCC1 (c.354T > C), NQO1 (c.559C > T), TPMT (c.719A > G) and XRCC1 (c.1196A > G) were polymorphic mutated. The patient died after three months of the second surgical treatment. **Conclusions:** We report for the first time a primary bladder malignant GCM accompanied by mutations in special driving genes such as EP300. We also conducted a comprehensive literature review and an in-depth discussion.

Keywords

Malignant Granular Cell Tumor, Bladder, Histopathology, EP300, Next-Generation High Throughput Sequencing

*Contribution equally.
#Corresponding author.

1. Background

Granular cell tumor (GCT) is a benign tumor thought to originate from nerve sheath cells. It accounts for about 2% of soft tissue tumors and could occur in any part of the body [1] [2] [3] [4] [5]. The most common sites are the mouth, skin, soft tissue, breast, and female reproductive organs. GCT occurred in the bladder is rare, and only a few cases have been reported [6] [7] [8] [9]. Malignant GCT is an extremely rare soft tissue malignant tumor, accounting for less than 2% of all soft tissue GCTs. Malignant GCT occurs in a wide range of ages, mostly in adults aged 30 - 70, with an average age of 50. Most of the clinical manifestations are painless masses in subcutaneous or deep soft tissue. Most of the cases occurred in the extremities, torso, head, neck, and breast [10]-[16]. To date, few cases of bladder malignant GCT have been reported [7] [17]. Few studies on the driving genes of malignant GCT, especially the specific driving genes of malignant GCT, are not clear [1] [18] [19]. Here, we report a case of malignant bladder GCT with vulvar, vaginal, and pelvic soft tissue invasion. Histopathology and IHC confirmed that it was a malignant GCT originating from the bladder. The next-generation high throughput sequencing detected several gene mutations, including a tumor-specific driving gene EP300 and another five genes associated with chemotherapy. We also conducted a literature review and in-depth discussion.

2. Case Presentation

The patient was a 45-year-old Chinese female, housewife and Han nationality. The patient found pelvic mass during physical examination a year ago, the clinical manifestations were intermittent lower abdominal discomfort, frequent urination, dysuria, no hematuria, no vaginal bleeding. The outpatient clinic was admitted to the hospital with "pelvic mass". The patient was without any treatment before. B-ultrasound examination showed that the left side of the uterus was abnormally hypoechoic (10.4 × 9.6 cm), the right ovary had no obvious abnormality, and the left ovary showed unclearly. Then she was admitted to the hospital as a "pelvic mass". The patient was treated with abdominal hysterectomy and double salpingectomy, pelvic tumor resection, cystectomy, and ureterostomy under general anesthesia.

Magnetic resonance imaging (MRI) pelvic plain scanning showed a large lobulated mass among the cervix, the anterior wall of the vagina, and below the bladder. The mass was 12 × 11 × 10 cm in size with clear boundary. T1W1 showed a slightly higher signal, T2W1 showed a high-low mixed-signal, and DWI showed a mixed high signal. An enhanced scan showed obvious uneven enhancement, uterine body, and cervical lifting. The bladder was connected tightly to the mass and compressed forward and upward (**Figure 1**). The mass in the pelvis was closely adhesive to the base of the bladder and the wall of the uterus. After complete hysterectomy, a huge mass was found between the anterior wall of the vagina and the posterior wall of the bladder. The anterior boundary of the

tumor was not separated from the posterior wall of the bladder and protruded into the bladder. When the bladder was completely dissociated from the extraperitoneal cavity, it was seen that the tumor originated from the posterior wall of the bladder and infiltrate to the anterior wall of the urethra to the pelvic floor.

Total cystectomy was performed, and the tumor with size of 11 × 11 × 4.5 cm was detected at the posterior wall of the bladder. The section of the tumor was grayish-yellow, tough, and lobulated. The tumor involved the whole layer of the bladder wall, did not break through the bladder adventitia, and the boundary between the tumor and the surrounding tissue was still clear (Figure 2).

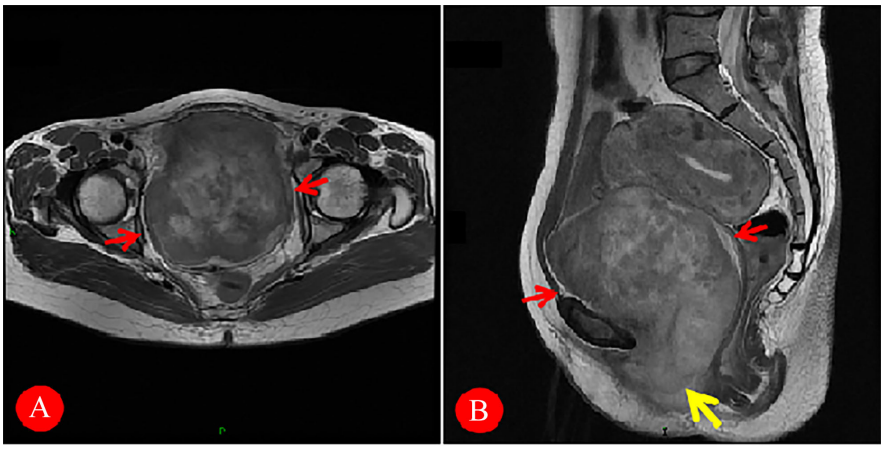

Figure 1. MRI showed a large mass between the cervix, the anterior wall of the vagina, and the bottom of the bladder, and the boundary was still clear. (A) A coronal section (The red arrow showed the extent of the tumor); (B) A sagittal section (the red arrow showed the extent of the tumor, the yellow arrow showed the connection between the tumor and the bottom of the bladder.).

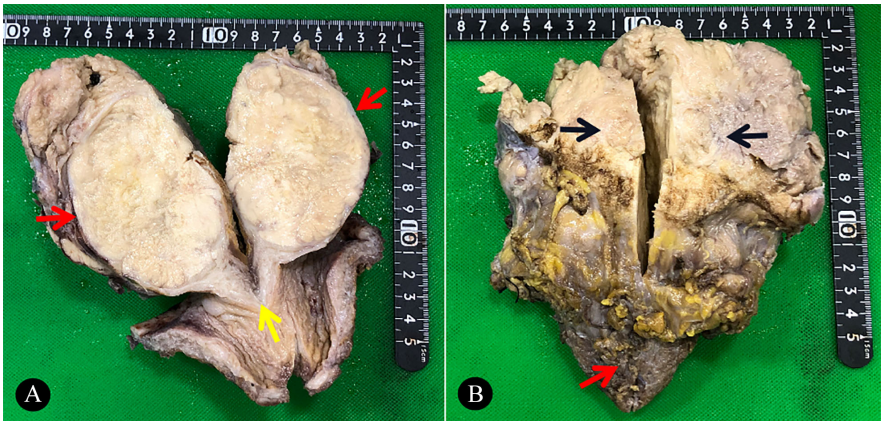

Figure 2. A volume of 11 × 11 × 4.5 cm in tumor size was collected to the posterior wall of the bladder. (A) The section of the tumor was grayish-yellow, tough, and lobulated. The red arrow showed the extent of the tumor, the yellow arrow showed the connection between the tumor and the bottom of the bladder. (B) Back view: The black arrow shows the adhesion between the tumor and the pelvic soft tissue. The red arrow showed the bottom of the bladder.

After surgical removal, hematoxylin and eosin (H&E) staining were performed on tumor tissue. The tumor tissue was separated by fibrous connective tissue, arranged in flake, nest and cord shape, showing infiltrative growth. The tumor cells were pleomorphic, round, polygonal, and fusiform. The ratio of the nucleus to the cytoplasm was increased. The cytoplasm was rich in red staining with a large number of eosinophilic bodies. The nuclei were heteromorphic with different sizes. Some of the nuclei were vacuolated and had obvious nucleoli. Multinucleated tumor cells and scattered coagulative necrotic foci were seen locally, and the mitotic figure was more than 5/50HPF (Figure 3).

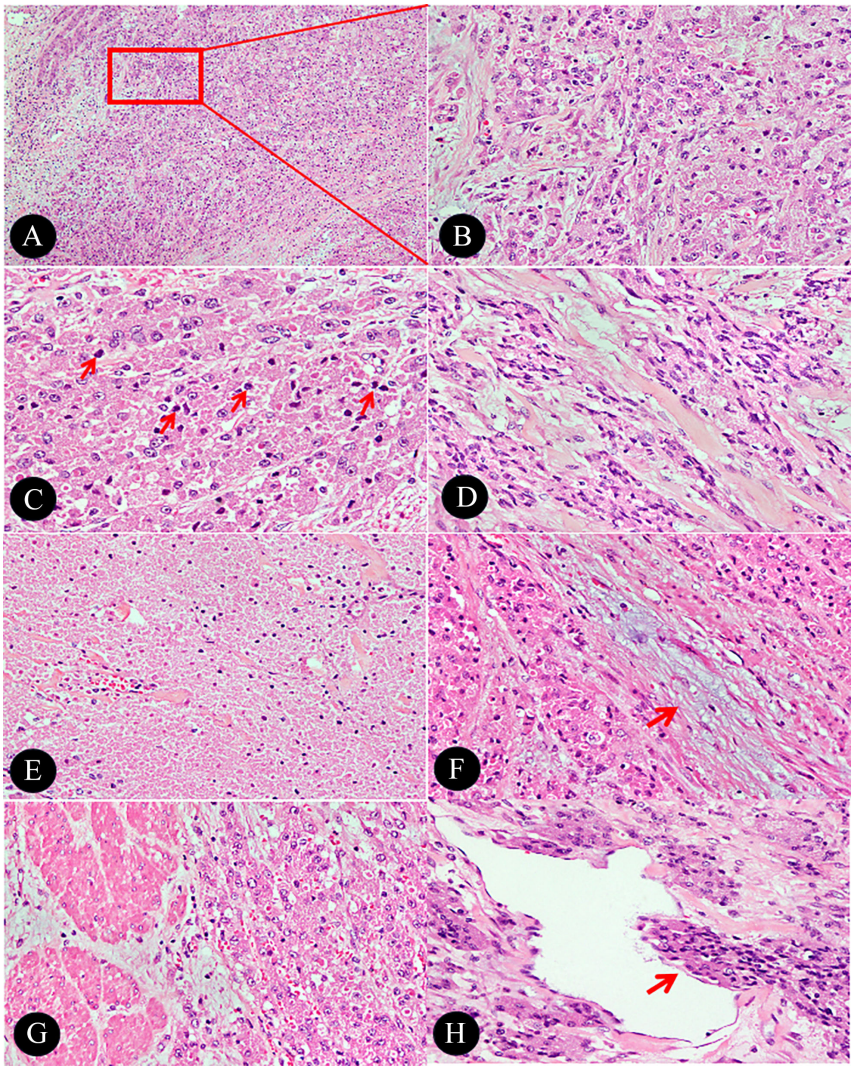

Figure 3. Under a microscope: (A) Overall the histopathology. (B) The tumor cells were pleomorphic, round, polygonal, and fusiform. The ratio of the nucleus to the cytoplasm was increased. The cytoplasm was rich in red staining with a large number of eosinophilic bodies. (C) The mitotic figure was more than 5/50HPF (shown by the red arrow). (D) The tumor tissue was separated by fibrous connective tissue, arranged in flake, nest and cord shape. (E) Coagulative necrosis. (F) Interstitial myxoid degeneration shown by the red arrow. (G) The tumor cells invaded the bladder muscle wall. (H) The tumor cells invade the lumen of blood vessels (shown by the red arrow).

DAKO company's latest Omnis automatic immunohistochemical instrument was used for staining, and the process was carried out under the operation manual provided by the manufacturer. The sources, clones, and manufacturer of the antibodies used are shown in Table 1. Negative and positive controls were all set up for each antibody. The IHC results showed that S-100, NSE, CD68, CR, *α*-AT, and TFE-3 in the tumor cells were strongly positive, and the Ki-67 proliferation index in most of the tumor areas was around 15% (Figure 4). The IHC results showed that SMA, Desmin, *α*-inhibin, GFAP, MyoD1, HMB45, and CK (pan) were all negative (not shown).

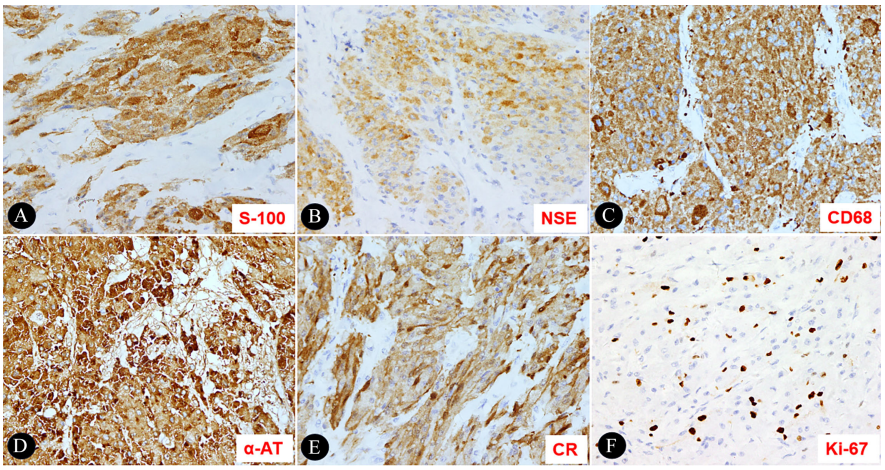

Figure 4. The IHC results showed that S-100 (A), NSE (B), CD68 (C), *α*-AT (D), CR (E), and TFE-3 in the tumor cells were strongly positive, and Ki-67 proliferation index in most of the tumor areas was around 15% (F).

Table 1. The sources, clones and manufacturer of the antibodies used in this study.

Antibodies	Clones	Manufacturers
CD68	KP1	MXB
NSE	3-3-C	MXB
S-100	4C4.9	MXB
CR(Calretinin)	MX027	MXB
***α*-AT(AAT)**	Polyclone	MXB
TFE-3	MRQ-37	MXB
SMA	1A4	MXB
Desmin	MX046	MXB
***α*-inhibin**	AMY82	MXB
GFAP	MX047	MXB
Ki-67	MIB-1	Dako
MyoD1	5.8A	MXB
HMB45	HMB45	MXB
CK(pan)	AE1/AE3	Dako

Next-generation high-throughput sequencing (NGS) covered 425 gene exons, fusion-related introns, variable splicing regions, specific microsatellite (MS) sites, and other common 1.46 Mb base sites were used in this study. The whole sequencing process was performed on the Illumina-based Hiseq 4000 Sequencing system at Nanjing Geneseeq Technology Inc., Nanjing, Jiangsu, China. In the sequencing of the 425 genes, the results of NGS indicated that the overall mutation rate is very low. The results revealed that the EP300 gene was missense mutated (c.457A > G) with 33% mutation abundance. The gene of EP300 is in the classification of "key genes in the tumor-related signaling pathways". The NGS results also showed that genes of DPYD (c.1627A > G), ERCC1 (c.354T > C), NQO1 (c.559C > T), TPMT (c.719A > G), and XRCC1 (c.1196A > G) were polymorphic mutated. These genes are all in the classification of "key genes for chemotherapy". The detailed locations and functions are shown in Table 2. NGS results also showed that the tumor mutational burden (TMB) was very lower (2.1 mutations/Mb), and the microsatellite (MS) analysis showed that no MIS-H related genes were detected. The list of the 425 genes and functional partition was shown in supplement data (Table 3).

Three months after the first operation, the patient was re-admitted to the hospital because of "vaginal mass found for more than one week". Specialist examination: a 3 cm lobulated moveable tenderness, clear boundary mass could be touched the right vaginal wall, and the mass was close to the orifice of the vulva. Surgical findings: the vulvar mass was located in the lower part of the vagina behind the right greater labia. It was a lobulated hard tumor, with a size of about 4 × 3 × 1 cm and clear boundary. The patient died three months after the second operation.

Table 2. The mulations of gens detected by NGS.

Genes	Variations	Mutant types	Ways of mutation	Possible functions
EP300	p.M153V	c.457A > G(p.M153V)	Missense mutation in exon 2 (33% in MF*)	Possible tumor driving genes
DPYD	p.I153V	c.1627A > G(p.I153V)	Heterozygous polymorphism	Side effects may increase for drugs of 5-FU, capecitabine, etc.
ERCC1	p.N118N	c.354T > C(p.N118=)	Heterozygous polymorphism	The curative effect by using drugs of platinum may be better than that of the wild type.
NQO1	p.P187S	c.559C > T(p.P187S)	Heterozygous polymorphism	The curative effect by using mitomycin C may be worse than that of the wild type.
TPMT	p.Y240C	c.719A > G(p.Y240C)	Heterozygous polymorphism	Toxic side effects by using mercaptopurine may increase
XRCC1	p.Q399R	c.1196A > G(p.Q399R)	Heterozygous polymorphism	The curative effect by using drugs of platinum may be better than that of the wild type.

*Mutation Frequency.

Table 3. Supplement data.

ABCB1(MDR1)	CDK12	ERCC2	IDH1	MSH6	PPARD	SMO
ABCC2(MRP2)	CDK4	ERCC3	IDH2	MTHFR	PPP2R1A	SOCS1
ADH1B	CDK6	ERCC4	IFNA6	MTOR	PRDM1	SOS1
AIP	CDK8	ERCC5	IFNB1	MUTYH	PREX2	SOX2
AKT1	CDKN1A	ESR1	IFNE	MYC	PRF1	SPOP
AKT2	CDKN1B	ETV1	IFNG	MYCL	PRKACA	SPRED1
AKT3	CDKN1C	ETV4	IFNGR1	MYCN	PRKAR1A	SPRY4
ALDH2	CDKN2A	ETV5	IFNGR2	MYD88	PRKCI	SRC
ALK	CDKN2B	ETV6	IGF1R	MYH9	PRKDC	SRSF2
AMER1	CDKN2C	EWSR1	IGF2	NAT1	PRSS1	SRY
APC	CEBPA	EXT1	IKBKE	NBN	PRSS3	STAG2
AR	CEP57	EXT2	IKZF1	NCOR1	PTCH1	STAT3
ARAF	CHD4	EZH2	IL7R	NF1	PTEN	STK11
ARID1A	CHD8	EZR	INPP4B	NF2	PTK2	STMN1
ARID1B	CHEK1	FANCA	IRF2	NFE2L2	PTPN11	SUFU
ARID2	CHEK2	FANCC	JAK1	NFKBIA	PTPN13	TACC3
ARID5B	CREBBP	FANCD2	JAK2	NKX2-1	QKI	TAP1
ASCL4	CRKL	FANCE	JAK3	NOTCH1	RAC1	TAP2
ASXL1	CSF1R	FANCF	JARID2	NOTCH2	RAC3	TEK
ATF1	CTCF	FANCG	JUN	NOTCH3	RAD50	TEKT4
ATIC	CTLA4	FANCI	KDM5A	NPM1	RAD51	TERC
ATM	CTNNB1	FANCL	KDR(VEGFR2)	NQO1	RAD51B	TERT
ATR	CUL3	FANCM	KEAP1	NRAS	RAD51C	TET2
ATRX	CUX1	FAT1	KIF1B	NRG1	RAD51D	TGFBR2
AURKA	CXCR4	FBXW7	KIT	NSD1	RAD54L	THADA
AURKB	CYLD	FGF19	KITLG	NTRK1	RAF1	TMEM127
AXIN2	CYP19A1	FGFR1	KLLN	NTRK2	RARA	TMPRSS2
AXL	CYP2A13	FGFR2	KMT2A(MLL)	NTRK3	RARG	TNFAIP3
B2M	CYP2A6	FGFR3	KMT2B	NUTM1	RASGEF1A	TNFRSF11A
BAD	CYP2A7	FGFR4	KMT2C	PAK3	RB1	TNFRSF14
BAI3	CYP2B6*6	FH	KMT2D(MLL2)	PALB2	RECQL4	TNFRSF19
BAK1	CYP2C19*2	FLCN	KRAS	PALLD	RELN	TNFSF11
BAP1	CYP2C9*3	FLT1(VEGFR1)	LHCGR	PARK2	RET	TOP1

Continued

BARD1	CYP2D6	FLT3	LMO1	PARP1	RHOA	TOP2A
BAX	CYP3A4*4	FLT4	LRP1B	PARP2	RICTOR	TP53
BCL2	CYP3A5	FOXA1	LYN	PAX5	RNF43	TP63
BCL2L11(BIM)	CYSLTR2	FOXL2	LZTR1	PBRM1	ROS1	TPMT
BCR	DAXX	FOXP1	MAP2K1(MEK1)	PDCD1(PD1)	RPTOR	TSC1
BIRC3	DDR2	FRG1	MAP2K2(MEK2)	PDCD1LG2(PD-L2)	RRM1	TSC2
BLM	DENND1A	GATA1	MAP2K4	PDE11A	RUNX1	TSHR
BMPR1A	DHFR	GATA2	MAP3K1	PDGFRA	RUNX1T1	TTF1
BRAF	DICER1	GATA3	MAP3K4	PDGFRB	SBDS	TUBB3
BRCA1	DLL3	GATA4	MAX	PDK1	SDC4	TYMS
BRCA2	DNMT3A	GATA6	MCL1	PGR	SDHA	U2AF1
BRD4	DOT1L	GNA11	MDM2	PHOX2B	SDHB	UGT1A1
BRIP1	DPYD	GNAQ	MDM4	PIK3C3	SDHC	VAMP2
BTG2	DTL(CDT2)	GNAS	MECOM	PIK3CA	SDHD	VEGFA
BTK	DUSP2	GRIN2A	MED12	PIK3CD	9-Sep	VHL
BUB1B	EGFR	GRM3	MEF2B	PIK3R1	SETBP1	WAS
c11orf30	EIF1AX	GRM8	MEN1	PIK3R2	SETD2	WISP3
CASP8	EP300	GSTM1	MET	PKHD1	SF3B1	WRN
CBL	EPAS1	GSTM4	MGMT	PLAG1	SGK1	WT1
CBLB	EPCAM	GSTP1	MITF	PLCB4	SKP2	XPA
CCND1	EPHA2	GSTT1	MLH1	PLK1	SLC34A2	XPC
CCNE1	EPHA3	HDAC2	MLH3	PMS1	SLC3A2	XRCC1
CD274(PD-L1)	EPHA5	HDAC9	MLLT1	PMS2	SMAD2	XRCC2
CD74	ERBB2(HER2)	HGF	MLLT3	POLD1	SMAD3	YAP1
CDA	ERBB2IP	HLA-A	MLLT4	POLD3	SMAD4	ZNF217
CDC73	ERBB3	HNF1A	MPL	POLE	SMAD7	ZNF703
CDH1	ERBB4	HNF1B	MRE11A	POLH	SMARCA4	
CDK10	ERCC1	HRAS	MSH2	POT1	SMARCB1	

Key genes for targeted drug use

Key genes for chemotherapy

Genetic risk prediction genes

Important tumor-driving genes, but there are no targeted drugs at present

Key genes in the tumor-related signaling pathways

3. Discussion and Conclusions

The diagnostic criteria for malignant GCT were proposed by Fanburg-Smith and his colleagues as early as 1998. Malignant histological criteria included coagulative necrosis, fusiform, vesicular nucleus of large nucleolus, increased mitotic activity (>2 mitoses/high magnification × 200), increased nuclear/cytoplasmic ratio, and pleomorphism [20]. According to the pathological criteria for the diagnosis of malignant GCT, both histopathology and immunohistochemical expression of this presented case support the diagnosis of malignant GCT [20]. In addition to the criteria of histopathology, in this case, we also identified biological changes associated with malignant characteristics, such as invasive growth and vascular invasion. The differential diagnosis of benign and malignant GCT is often tricky in both pathology and clinic. However, this case is not difficult, based on histopathology and biological behavior. The tumor originated from the bladder wall and invaded the muscular layer of the bladder. In addition, the tumor also widely invaded into vagina, cervix, and soft tissues in the pelvic, showing extremely malignant biological behavior. The patient did not respond to chemotherapy and died three months after the second operation.

Malignant GCM is extremely rare, and few cases have been reported [7] [11] [17] [21] [22]. So far, we know little about the molecular biology and molecular genetics of malignant GCT. Recently, Richard Davis *et al.* reported a case of malignant GCT of the lung with ATM gene mutation. ATM gene encodes DNA repair protein involved in cell cycle regulation [1]. Xu and colleagues apply the NGS to identify mutations in the genes of ASXL, NOTCH, and PARP pathways as potential driver mutations in pulmonary malignant GCT [23].

In our case, based on the high-throughput second-generation sequencing of 425 genes, the overall mutation rate of the tumor was very low. In the classification of "the key genes in tumor-related signaling pathway", the EP300 gene was missense mutated (C.457A > G) with 33% mutation abundance. As we know, EP300 gene is located on chromosome 22, and encodes adenovirus E1A-related intracellular p300 protein, which has acetyltransferase activity, regulates transcriptional activity through chromosome remodeling. EP300 and its homolog CREB binding protein (CBP) are two lysine acetyltransferases, which act as transcriptional factors and play an essential role in developing, progression, and treating many diseases, especially in tumors. Some cancer-related point mutations are gain-of-function alterations in EP300/CBP that might also contribute to cancer development [24] [25] [26]. It has been found that the inactivation mutations of histone acetyltransferase CBP and EP300 are prevalent in diffuse large B cell lymphoma (DLBCL). The functional inactivation mutations of CBP and EP300 will down-regulate the expression of CD20, which leads to the failure of anti-CD20 antibody therapy [27]. Other studies have also shown that targeting EP300 may effectively treat fatal leukemia [28]. Therefore, the use of synthetic small-molecular compounds to inhibit the function of mutant EP300 brings hope for targeted therapy of malignant tumors [29]. A recent study also shows that the

EP300 protein is related to the grade, pathological T stage, lymph node metastasis, and survival rate of esophageal squamous cell carcinoma [30].

Gongmin Zhu and colleagues found that EP300 mutation in bladder cancer is associated with a higher tumor mutation burden (TMB) and up-regulates the immune system's signal pathway, which can be used as a biomarker to predict the effect of immunotherapy [31]. In our case, NGS results showed that the TMB was significantly lower (2.1 mutations/Mb). The relationship between EP300 mutation and TMB may be related to different tumor types and mutation sites. How genetic or epigenetic changes in EP300 will affect the phenotype of various cancers is far from clear.

In our case, in addition to the EP300 missense mutation, it was also detected that DPYD, NQO1 and TPMT had heterozygous polymorphism mutations; ERCC1 and XRCC1 had homozygous polymorphism mutations. These genes are all in the classified as "the key genes for chemotherapy" in total 425 genes. Heterozygous mutation of the DPYD gene in p. I543V is a missense mutation caused by single nucleotide polymorphism rs1801159, which can decrease the activity of DPYD, increase the toxicity and side effects of 5-fluorouracil, and increase the risk of vomiting and nausea in patients [32]. ERCC1 gene p.N118N homozygous mutation is a synonymous mutation caused by single nucleotide polymorphism rs11615. This homozygous genotype can increase the risk of lung cancer and breast cancer. Besides, this mutation can reduce mRNA level by affecting the stability of ERCC1 transcripts and increase cell response to platinum drugs by reducing DNA repair function [33]. TPMT gene p.Y240C heterozygous mutation (TPMT*3C) is a missense mutation caused by single nucleotide polymorphism rs1142345. This heterozygous polymorphism mutation can reduce mercaptopurine methyltransferase activity by about 50%, which leads to serious poor metabolism of mercaptopurine and side effects [34]. XRCC1 gene p.Q399R homozygous mutation is a missense mutation caused by single nucleotide polymorphism rs25487, which is associated with the risk of non-small cell lung cancer, breast cancer, colorectal cancer, gastric cancer, and other tumors. This homozygous mutation is related to platinum chemotherapeutic drugs' efficacy and can increase the response rate of cells to platinum drugs [35].

There is no targeted drug for malignant GCT, and whether it is sensitive to chemotherapy may be related to its particular gene mutation. Wei, L, and colleagues performed whole-genome sequencing of a malignant GCT that was metabolically responsive to pazopanib. The results showed that the mutation rate was shallow, and the whole genome was stable [19]. Due to the small number of cases, there are not many reports on the survival of malignant GCM. However, it is generally believed that prognosis of GCM is closely related to the tumor's size, local invasion, and distant metastasis [22] [36]. It took less than a year from discovery to death in our case.

In summary, few cases of malignant GCM of the bladder have been reported, but none of them have been studied by molecular genetics. We performed mo-

lecular genetic analysis of malignant GCM of the bladder for the first time, and in particular, detected a missense mutation in exon 2 of EP300 gene p.M153V with a high mutation abundance. The clinical significance of EP300 gene mutation in malignant GCM of the bladder is not clear. Whether it leads to the EP300 protein dysfunction to activate downstream signal pathways and participates in tumorigenesis and development are not certified. More clinical cases and experimental studies are needed for further exploration.

Declarations

Ethics Approval and Consent to Participate

This case was reviewed and approved by the Ethics Committee of Affiliated Hospital, Guangdong Medical University, Zhanjiang, China.

Consent for Publication

Written informed consent was obtained from the patient's next of kin 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.

Availability of Data and Materials

All data generated and described in this article are freely available to any scientist wishing to use them for noncommercial purposes, without breaching participant confidentiality.

Authors' Contributions

J.H. found the specific case; J.H. and B.H., two senior diagnostic pathologist made the final pathological diagnosis for the case; J.H. and D.Z. wrote the main manuscript text; D.Z., XL.R., Y.L. and J.H. prepared Figures 1-4; All authors reviewed the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Davis, R., Deak, K. and Glass, C.H. (2019) Pulmonary Granular Cell Tumors: A Study of 4 Cases Including a Malignant Phenotype. *The American Journal of Surgical Pathology*, **43**, 1397-1402. https://doi.org/10.1097/PAS.0000000000001303

[2] Stemm, M., *et al.* (2017) Typical and Atypical Granular Cell Tumors of Soft Tissue: A Clinicopathologic Study of 50 Patients. *American Journal of Clinical Pathology*, **148**, 161-166. https://doi.org/10.1093/ajcp/aqx058

[3] Rubino, F., *et al.* (2020) Granular Cell Tumors of the Sellar Region: What Should Be Done after Subtotal Resection? A Systematic Review. *Pituitary*, **23**, 721-732. https://doi.org/10.1007/s11102-020-01068-6

[4] Aoyama, K., *et al.* (2012) Granular Cell Tumors: A Report of Six Cases. *World Journal*

of Surgical Oncology, **10**, Article No. 204. https://doi.org/10.1186/1477-7819-10-204

[5] Shi, Y., *et al.* (2020) Experience with Esophageal Granular Cell Tumors: Clinical and Endoscopic Analysis of 22 Cases. *Digestive Diseases and Sciences*, **66**, 1233-1239. https://doi.org/10.1007/s10620-020-06337-9

[6] Lee, C., *et al.* (2018) Clinicopathologic Features of Benign Neurogenic Tumor of Urinary Bladder. *International Journal of Surgical Pathology*, **26**, 221-228. https://doi.org/10.1177/1066896917742722

[7] Sun, Y., *et al.* (2018) Granular Cell Tumor of the Bladder: A Report of Six Cases. *Urology*, **121**, 203.e1-203.e5. https://doi.org/10.1016/j.urology.2018.08.018

[8] Yoshida, T., *et al.* (2001) Granular Cell Tumor of the Urinary Bladder. *International Journal of Urology*, **8**, 29-31. https://doi.org/10.1046/j.1442-2042.2001.00241.x

[9] Eandi, J.A., *et al.* (2007) Granular Cell Tumor of the Urinary Bladder with Pseudoepitheliomatous Hyperplasia and Colocalization with Adenocarcinoma. *International Journal of Urology*, **14**, 862-864. https://doi.org/10.1111/j.1442-2042.2007.01827.x

[10] Shah, K., *et al.* (2020) Malignant Granular Cell Tumor of the Lower Extremity in an Adolescent Male. *Journal of Pediatric Hematology/Oncology*, **43**, e529-e531. https://doi.org/10.1097/MPH.0000000000001886

[11] Stasek, M., *et al.* (2020) Malignant Granular Cell Tumor of the Esophagus: A Case Report. *Annals of Thoracic and Cardiovascular Surgery*, **26**, 359-364. https://doi.org/10.5761/atcs.cr.20-00117

[12] Bradford, B.E., *et al.* (2020) Benign and Malignant Granular Cell Tumor of the Hypopharynx: Two Faces of a Rare Entity. *Head and Neck Pathology*, **15**, 281-287. https://doi.org/10.1007/s12105-020-01157-9

[13] Tsukamoto, S., *et al.* (2019) Malignant Granular Cell Tumor of the Median Nerve: A Case Report with a Literature Review of 157 Cases. *Skeletal Radiology*, **48**, 307-316. https://doi.org/10.1007/s00256-018-3017-2

[14] Jia, X., *et al.* (2017) Large Malignant Granular Cell Tumor with Suprascapular Nerve and Brachial Plexus Invasion: A Case Report and Literature Review. *Medicine* (*Baltimore*), **96**, e8531. https://doi.org/10.1097/MD.0000000000008531

[15] Akahane, K., *et al.* (2015) Malignant Granular Cell Tumor of the Breast: Case Report and Literature Review. *Breast Cancer*, **22**, 317-323. https://doi.org/10.1007/s12282-012-0362-1

[16] Liu, T.T., *et al.* (2015) Primary Cutaneous Malignant Granular Cell Tumor: A Case Report in China and Review of the Literature. *Diagnostic Pathology*, **10**, Article No. 113. https://doi.org/10.1186/s13000-015-0357-2

[17] Zhuang, Y.Z., Jiang, X.Y. and Chen, P.Q. (2006) Malignant Granular Cell Tumor of the Urinary Bladder. *Chinese Journal of Pathology*, **35**, 188.

[18] Pareja, F., *et al.* (2018) Loss-of-Function Mutations in ATP6AP1 and ATP6AP2 in Granular Cell Tumors. *Nature Communications*, **9**, Article No. 3533. https://doi.org/10.1038/s41467-018-05886-y

[19] Wei, L., *et al.* (2015) Whole-Genome Sequencing of a Malignant Granular Cell Tumor with Metabolic Response to Pazopanib. *Cold Spring Harbor Molecular Case Studies*, **1**, a000380. https://doi.org/10.1101/mcs.a000380

[20] Fanburg-Smith, J.C., *et al.* (1998) Malignant Granular Cell Tumor of Soft Tissue: Diagnostic Criteria and Clinicopathologic Correlation. *The American Journal of Surgical Pathology*, **22**, 779-794. https://doi.org/10.1097/00000478-199807000-00001

[21] Quinn, P.L., *et al.* (2019) Malignant Granular Cell Tumor of the Bile Duct. *ACG*

Case Reports Journal, **6**, e00193. https://doi.org/10.14309/crj.0000000000000193

[22] Moten, A.S., *et al.* (2018) Malignant Granular Cell Tumor: Clinical Features and Long-Term Survival. *Journal of Surgical Oncology*, **118**, 891-897. https://doi.org/10.1002/jso.25227

[23] Xu, S., *et al.* (2015) Next Generation Sequencing Uncovers Potential Genetic Driver Mutations of Malignant Pulmonary Granular Cell Tumor. *Journal of Thoracic Oncology*, **10**, e106-e109. https://doi.org/10.1097/JTO.0000000000000640

[24] Attar, N. and Kurdistani, S.K. (2017) Exploitation of EP300 and CREBBP Lysine Acetyltransferases by Cancer. *Cold Spring Harbor Perspectives in Medicine*, **7**, a026534. https://doi.org/10.1101/cshperspect.a026534

[25] Breen, M.E. and Mapp, A.K. (2018) Modulating the Masters: Chemical Tools to Dissect CBP and p300 Function. *Current Opinion in Chemical Biology*, **45**, 195-203. https://doi.org/10.1016/j.cbpa.2018.06.005

[26] Blobel, G.A. (2000) CREB-Binding Protein and p300: Molecular Integrators of Hematopoietic Transcription. *Blood*, **95**, 745-755. https://doi.org/10.1182/blood.V95.3.745.003k05_745_755

[27] Scialdone, A., *et al.* (2019) Depletion of the Transcriptional Coactivators CREB-Binding Protein or EP300 Downregulates CD20 in Diffuse Large B-Cell Lymphoma Cells and Impairs the Cytotoxic Effects of Anti-CD20 Antibodies. *Experimental Hematology*, **79**, 35-46.e1. https://doi.org/10.1016/j.exphem.2019.10.004

[28] Huang, Y., *et al.* (2019) The Leukemogenic TCF3-HLF Complex Rewires Enhancers Driving Cellular Identity and Self-Renewal Conferring EP300 Vulnerability. *Cancer Cell*, **36**, 630-644.e9. https://doi.org/10.1016/j.ccell.2019.10.004

[29] Yang, Y., *et al.* (2020) Discovery of Highly Potent, Selective, and Orally Efficacious p300/CBP Histone Acetyltransferases Inhibitors. *Journal of Medicinal Chemistry*, **63**, 1337-1360. https://doi.org/10.1021/acs.jmedchem.9b01721

[30] Bi, Y., *et al.* (2019) EP300 as an Oncogene Correlates with Poor Prognosis in Esophageal Squamous Carcinoma. *Journal of Cancer*, **10**, 5413-5426. https://doi.org/10.7150/jca.34261

[31] Zhu, G., *et al.* (2020) EP300 Mutation Is Associated with Tumor Mutation Burden and Promotes Antitumor Immunity in Bladder Cancer Patients. *Aging* (*Albany NY*), **12**, 2132-2141. https://doi.org/10.18632/aging.102728

[32] Zhang, H., *et al.* (2007) DPYD*5 Gene Mutation Contributes to the Reduced DPYD Enzyme Activity and Chemotherapeutic Toxicity of 5-FU: Results from Genotyping Study on 75 Gastric Carcinoma and Colon Carcinoma Patients. *Medical Oncology*, **24**, 251-258. https://doi.org/10.1007/BF02698048

[33] Nebert, D.W., *et al.* (2002) NAD(P)H: Quinone Oxidoreductase (NQO1) Polymorphism, Exposure to Benzene, and Predisposition to Disease: A HuGE Review. *Genetics in Medicine*, **4**, 62-70. https://doi.org/10.1097/00125817-200203000-00003

[34] Almoguera, B., *et al.* (2014) Imputation of TPMT Defective Alleles for the Identification of Patients with High-Risk Phenotypes. *Frontiers in Genetics*, **5**, 96. https://doi.org/10.3389/fgene.2014.00096

[35] Li, D., *et al.* (2007) Effects of Base Excision Repair Gene Polymorphisms on Pancreatic Cancer Survival. *International Journal of Cancer*, **120**, 1748-1754. https://doi.org/10.1002/ijc.22301

[36] Alnashwan, Y.A., Ali, K. and Amr, S.S. (2019) Metastasizing Malignant Granular Cell Tumor (Abrikossoff Tumor) of the Anterior Abdominal Wall, with Prolonged Survival. *Case Reports in Pathology*, **2019**, Article ID: 9576487. https://doi.org/10.1155/2019/9576487

Abbreviations

GCT: Granular cell tumor
NGS: Next-generation high throughput sequencing
MRI: Magnetic resonance imaging
IHC: Immunohistochemistry
H&E: Hematoxylin and Eosin
MS: Microsatellite
TMB: Tumor Mutational Burden
CBP: CREB binding protein
DLBCL: Diffuse large B cell lymphoma