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Case Report

A rare and easily misdiagnosed tumor of the urinary bladder: primary composite pheochromocytoma

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Abstract: Background: Composite pheochromocytoma, which is a tumor composed of ordinary pheochromocytoma and other components, is extremely rare in bladder. We present a case of this rarely seen tumor in bladder, and discuss the clinical features, behavior, pathologic findings, essentials of diagnosis and prognosis of this tumor after literature review. Methods: Specimens from a 55-year-old woman with primary composite pheochromocytoma in bladder were analyzed by immunohistochemical (IHC) and fluorescence in situ hybridization (FISH). Clinicopathological characteristics were also collected and discussed. Then, we searched and reviewed literatures related with composite pheochromocytoma that were published in PubMed over the last 80 years. Results: B-mode ultrasound scanner and Magnetic Resonance Imaging (MRI) detected a papillary and infiltrative tumor mass in the irregularly thickened posterior walls of the urinary bladder. Histologically, the tumor showed evidence of big ganglion-liked cells and small round cells in cystoscopy biopsy and typical "Zellballen" structure in gross specimen. On PubMed, a total of 58 cases of composite pheochromocytoma has been reported during 1933-2017. Conclusion: Composite pheochromocytoma in urinary bladder, which has distinctive clincopathologic features, is an extremely rare disease and can only be diagnosed by pathologists. Diagnosis is difficult before histopathological examination and should be considered in patients with no risk factors for usual bladder tumor. The rate of metastasis and death is higher in cases where the second component is not ganglioneuroma. Fortunately, treatment of this type of tumor remains the same as pheochromocytoma. Patients with localized tumors have an extremely favorable prognosis.

Keywords: Composite pheochromocytoma, ganglioneuroma, bladder, primary, diagnosis, IHC, FISH

Introduction

Pheochromocytoma is a kind of neuroendocrine tumor that usually develops ahead of the chromaffin cells of the adrenal medulla [1]. Extra-adrenal pheochromocytomas (paragangliomas) are closely related tumors that originate from the ganglia of the sympathetic nervous system. The pheochromocytoma of the urinary bladder accounts for less than 1% of the overall incidence of pheochromocytomas and less than 0.06% of the bladder tumors [2]. As to composite pheochromocytoma, it is an extremely rare tumor composed of ordinary pheochromocytoma and other components which are mostly neuroblastic elements in bladder. We present within this article an adult woman diagnosed of non-functional composite paraganglioma in bladder. Furthermore, we concluded the clinicopathologic features and other characteristics of composite paraganglioma after literature review.

Materials and methods

The patient was contacted by telephone to obtain verbal informed consent.

The 55 years old female patient was initially admitted to Guangzhou General Hospital of Guangzhou Military Area Command of Chinese PLA. The clinical manifestations and neuroimaging examinations was obtained by reviewing the medical records. The IHC staining and FISH

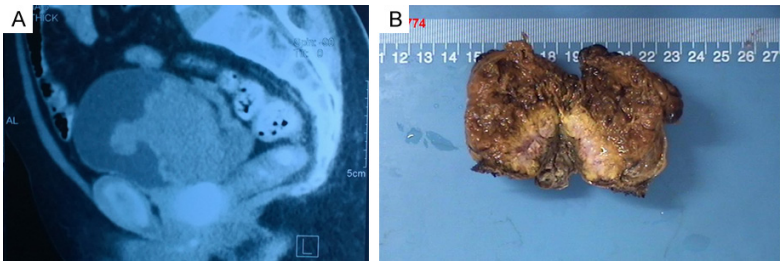

Figure 1. A: MRI showed tumor was papillary and infiltrative, locating in the irregularly thickened posterior walls of the urinary bladder. B: Macroscopic findings: the cut surface of the tumor was soft, gray-yellow with focal hemorrhage.

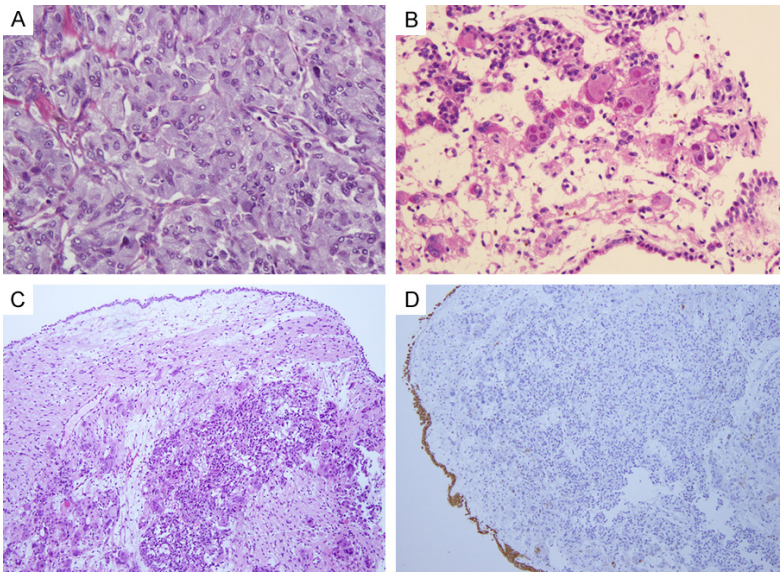

Figure 2. A: The area of pheochromocytoma showed the nested arrangement of cells (Zellballen) and stippled chromatin (×200). B: Histologic appearance of ganglioneuroblastoma portion of the tumor, showing ganglion cell (middle part of the picture) under the urothelium and the small round cells with hyperchromatic nuclei, such as lymphocyte-like cells in the top part of the picture (×200). C: The area of ganglioneuroma (×40). D: IHC CK staining showed clear visualization of urothelial lining (×40).

detection was performed using a standard technique as demonstrated previously [3]. Formalin-fixed, paraffin-embedded sections were stained with hematoxylin and eosin (H&E) for routine histological evaluation. Additional 4-micrometer-thick sections were mounted on electrostatic slides and used for IHC staining. The slides were stained using the EnVision method and commercially available monoclonal and polyclonal antibodies. The primary antibodies against the following antigens were used: NEU-N (Dako, 1:200 dilution), SYN (Dako, 1:200 dilution), CGA (Dako, 1:200 dilution), NSE (Dako, 1:200 dilution), S-100 (Dako, 1:200 dilution), NF (Dako, 1:200 dilution), Ki-67 (Dako, 1:200 dilution); and CD68 (Dako, 1:200 dilution). Then, using the online database PubMed, we analyzed the related literature published over the last 80 years.

Results

Clinical features

A 55-year-old woman was admitted to PLA hospital for a chief complain of hematuria and pollakiuria for 3 months. Then type-B ultrasonic checks detected an abnormal papillary mass in the bladder. Blood tests were within normal limits. Magnetic resonance imaging (MRI) and computerized tomography (CT) showed a papillary and infiltrative tumor mass measuring 6.2*5.9 cm in the irregularly thickened posterior walls of the urinary bladder (**Figure 1A**). Moreover, PET-CT confirmed that it was a primary bladder mass with no evidence of metastases. It was suspicious of bladder papillary urothelial neoplasm based on the clinical manifestations. Then, the patient was sent to the department of endoscopy to have a cystoscopy and biopsy, Microscopic morphology suggests primary bladder ganglioneuroblastoma/ganglioneuroma due to the limited tissue consisting of ganglion-like cells and neuroblastoma-like cells. At last, the patient was transferred to urology department to have the tumor resected in surgery. The postoperative course was uneventful.

Pathological findings

Cystoscopy biopsy specimen: Histologically, the tissue was small and crushed. It was like a ganglioneuroblastoma [4] and distinctively showed evidence of both maturation (gangliocyte) and

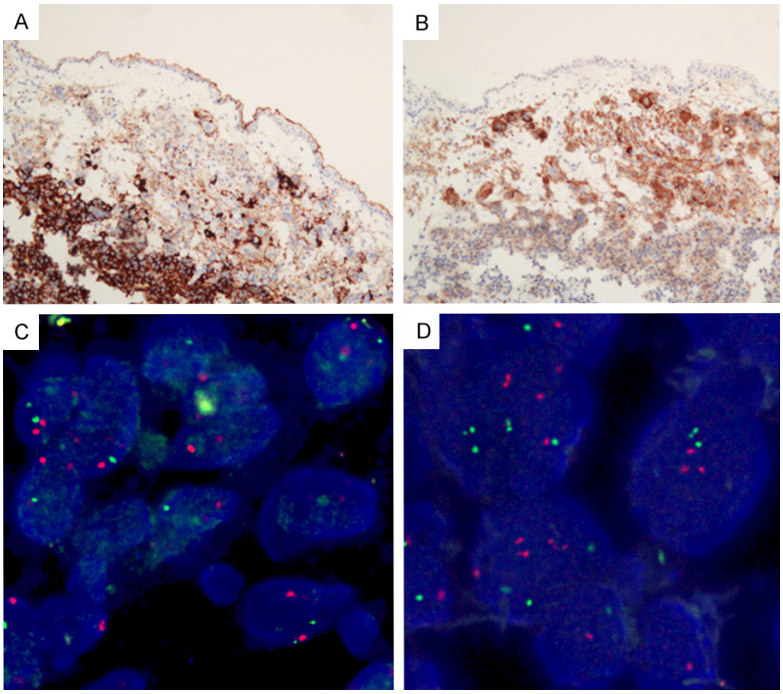

Figure 3. A: The chromaffin cells were strongly positive for CGA, but the ganglion cells were negative or weakly positive for CGA (×100). B: SYN expression pattern was complementary. The ganglion cells were strong positive but the chromaffin cells were weak (×100). C: N-MYC gene amplification by FISH: No amplification (N-MYC: CEP2 <2.0). D: Deletion in short arm of 1p by FISH: No deletion (1p/1q ratio >0.88).

involution (neuroblastoma). Maturation appeared to be occurring under the urothelium in a centrifugal manner in which ganglion cells and neuroblasts intermingled (**Figure 2B**). To be specific, large cells showed round open nuclei, prominent nucleoli and cytoplasm that were predominantly eosinophilic. These cells had the appearance of ganglion cells and they were below the urothelium. In the center area, it composed predominantly of small cells with round or oval hyperchromatic nuclei, with no nucleoli and very little cytoplasm. However, mitotic figures were rarely present and IHC staining showed that Ki-67 index was only 3%-5% in the section and small round cells are CGA positive. Notably, the big ganglion-like cells are NEU-N and S100 positive, while the SYN and CGA expression are characteristically complementary in these two different types of cell with distinct histological characteristics (**Figure 3A**, **3B**). To be specific, small cells are "Syn (partly +), CgA (strong +)", while large cells are "Syn (strong +), CgA (partly +)". FISH test showed no amplification of N-MYC and no deletion of 1P (**Figure 3C**, **3D**). Taken together, we diagnosed the biopsy as ganglioneuroma.

Bladder tumor gross specimen: General view: The tumor was measured 6.2 by 6 by 2.5 cm. It was soft and the cut surface was gray-yellow with focal hemorrhage (**Figure 1B**).

Histologically: Two different components could be seen: one component consisted of cells with round or oval nuclei and were mostly arranged in irregular small nests (Zellballen) (**Figure 2A**). The cytoplasm is fine granular, basophilic or amphophilic, while mitosis was rare. The other component was just like the former biopsy with big ganglion cells and small round blue cells. And in the background, Schwann cells were aligned in bundles or interwoven arranged (**Figure 2C**, **2D**). As to the IHC staining results, tumor cells in the Zellballen areas are strongly positive for CgA and Syn, while big ganglion cells are positive for NEU-N. And scattered spindle cells were positive for S-100.

Taken together, the final diagnosis was primary composite pheochromocytoma of bladder. This case was quite thought-provoking, as it gave us a warning that we should be careful and discreet with the diagnosis of this entity in small biopsy specimen due to the limited information.

Literature review

The first case of composite pheochromocytoma was diagnosed and reported in 1933 by Hick et al [5]. And after that, sporadic case reports were published occasionally. By searching the PubMed database online, we found a total of 58 reported cases of composite pheochromocytoma from 1933 to 2017 worldwide, including America, Northern Europe, Japan and China. Among them, Most reported cases came from the United States of America, indicating a higher incidence of composite pheochromocytoma

Table 1. Summary of reported composite pheochromocytomas

Authors	Year	Age	Sex	Location	Treatment	Metastasis	Follow-up	Status
Robinet G, et al [23]	2017	61	Male	Adrenal gland	N/A	N/A	N/A	N/A
Yamasaki M, et al [24]	2017	59	Male	Left adrenal gland	Resection	Yes	N/A	N/A
Namekawa T, et al [25]	2016	42	Male	Left adrenal gland	Resection	No	2.5 years	Survival
Shida, et al [13]	2015	29	Female	Left adrenal gland	Resection	No	2 years	Survival
Shida, et al [13]	2015	59	Male	Left adrenal gland	N/A	N/A	N/A	N/A
Shida, et al [13]	2015	53	Male	Right adrenal gland	Resection	No	6 years	Survival
Gupta, et al [26]	2014	50	Male	Pancreas	Resection	No	6 days	Dead
Rao, et al [16]	2013	37	Female	Left adrenal gland	Resection	No	N/A	N/A
Rai, et al [27]	2012	40	Female	Left adrenal gland	Resection	No	5 days	Survival
Kikuchi, et al [21]	2012	12	Female	Right adrenal gland	Conservative therapy	Yes	1 year	Dead
Majumder S, et al [28]	2012	34	Female	Pancreas	Resection	No	7 days	Survival
Ende, et al [29]	2012	45	Female	Left adrenal gland	Resection	No	N/A	N/A
Menon, et al [30]	2011	27	Male	Left adrenal gland	N/A	N/A	N/A	N/A
Khan, et al [5]	2010	61	Male	Right adrenal gland	Resection	No	N/A	N/A
Thiel, et al [31]	2010	9	Female	Right adrenal gland	Resection	No	18 months	Survival
Gong, et al [32]	2010	50	Male	Retroperitoneal mass	N/A	N/A	N/A	N/A
Gong, et al [32]	2010	36	Male	Right adrenal mass	N/A	N/A	N/A	N/A
Comstock, et al [15]	2009	15	Male	Right adrenal gland	Resection	No	N/A	Survival
Ch'Ng, et al [20]	2007	37	Female	Left adrenal gland	Resection	Yes	28 years	Dead
Tohme, et al [33]	2006	41	Female	Retroperitoneum	Resection	No	1 year	Survival
Choi, et al [34]	2006	48	Male	Left adrenal gland	Resection	No	8 months	Survival
Tatekawa, et al [35]	2006	5	Male	Left adrenal gland	Resection	No	N/A	N/A
Onozawa, et al [36]	2005	47	Female	Left adrenal gland	Resection	No	N/A	N/A
Okumi, et al [37]	2003	55	Female	Right adrenal gland	Resection	No	1 year	Survival
Pathmanathan, et al [38]	2003	73	Male	Left adrenal gland	Resection	Yes	N/A	N/A
Satake, et al [39]	2001	59	Female	Right adrenal gland	Conservative therapy	Yes (bone and lung)	3 months	Dead
Fujiwara, et al [40]	2000	29	Female	Left adrenal gland	Resection	No	5 years	Survival
Lam, et al [41]	1999	32	Male	Right adrenal gland	Incidental finding at autopsy	N/A	N/A	Dead
Lam, et al [41]	1999	52	Male	Right adrenal gland	Incidental finding at autopsy	N/A	N/A	Dead
Lam, et al [41]	1999	73	Female	Right adrenal gland	Incidental finding at autopsy	N/A	N/A	Dead
Lam, et al [41]	1999	75	Female	Right adrenal gland	Incidental finding at autopsy	N/A	N/A	Dead
Juarez, et al [42]	1999	69	Female	Right adrenal gland	Resection	No	14 months	Survival
Umemoto, et al [43]	1998	67	Male	Right adrenal gland	Resection	N/A	N/A	N/A

Matias-Guiu, et al [44]	1998	49	Male	Left adrenal gland	Incidental finding at autopsy	N/A	N/A	Dead
Brady, et al [45]	1997	34	Male	Left adrenal gland	Resection	N/A	N/A	N/A
Radin, et al [46]	1997	76	Female	Left adrenal gland	N/A	N/A	N/A	N/A
Radin, et al [46]	1997	72	Female	Left adrenal gland	N/A	N/A	N/A	N/A
Sakaguchi, et al [47]	1996	48	Male	Bilateral adrenal gland	Radiotherapy & Chemotherapy	Yes	3 months	Dead
Moore, et al [48]	1995	66	Female	Left adrenal gland	Resection	No	30 months	Survival
Watanabe, et al [49]	1995	42	Male	Left adrenal gland	Resection	No	N/A	Survival
Watanabe, et al [49]	1995	35	Male	Right adrenal gland	Resection	No	N/A	Survival
Chetty, et al [50]	1993	61	Female	Bilateral adrenal gland	Resection	No	N/A	Survival
Nagashima, et al [51]	1993	48	Female	Right adrenal gland	Resection	No	N/A	N/A
Kimura N, et al [52]	1991	35	Male	Adrenal gland	Resection	No	N/A	Survival
Kimura N, et al [52]	1991	21	Female	Retroperitoneal	Resection	No	N/A	Survival
Elliott, et al [5]	1989	47	Male	Left adrenal gland	Resection	No	18 months	Survival
Balazs, et al [5]	1988	37	Female	Right adrenal gland	Resection	No	2 years	Survival
Aiba, et al [53]	1988	53	Male	Right adrenal gland	Resection	No	N/A	Survival
Salmi, et al [5]	1988	65	Female	Right adrenal gland	Resection	No	N/A	Survival
Min, et al [54]	1988	39	Female	Left adrenal gland	Resection	N/A	N/A	Dead
Nigawara, et al [55]	1987	43	Male	Right adrenal gland	Resection	Yes	N/A	Dead
Tischler, et al [56]	1987	25	Male	Right adrenal gland	Resection	No	N/A	Survival
Nakagawara, et al [57]	1985	14	Female	Right adrenal gland	Chemotherapy	Yes	6 months	Dead
Choutet, et al [58]	1981	58	Male	Left adrenal gland	N/A	N/A	N/A	N/A
Trump, et al [5]	1977	40	Female	Left adrenal gland	Resection	No	1 year	Survival
Dawson, et al [5]	1969	66	Female	Right adrenal gland	Resection	No	1 year	Survival
Rosenthal, et al [5]	1936	52	Male	Bilateral adrenal gland	Incidental finding at autopsy	N/A	N/A	N/A
Hick, et al [5]	1933	64	Female	Left adrenal gland	Incidental finding at autopsy	N/A	N/A	N/A

in the white people. The average age at diagnosis was 46 years and the male to female ratio of cases was 1:1, including 29 male (mean age 44 years, range 5-73 years) and 29 female (mean age 47 years, range 9-76 years) (**Table 1**).

Discussion

Composite phaeochromocytoma, mostly localized in the adrenal gland, is also known as mixed neuroendocrine-neural tumor that is composed of phaeochromocytoma and other neural crest derivatives. The non-phaeochromocytoma component includes ganglioneuroma, ganglioneuroblastoma, neuroblastoma, malignant peripheral nerve sheath tumor and neuroendocrine carcinoma. The incidence of this rare tumor is reported to be 3% in sympathoadrenal pheochromocytomas/paragangliomas [6]. However, pheochromocytomas in bladder is extremely rare and only accounts for 0.06% of all types of tumors in bladder and 6% of extra-adrenal pheochromocytomas [2, 7]. In addition, the urinary bladder is the most common primary site for pheochromocytomas/paragangliomas (79.2%) in the genitourinary tract, followed by the urethra (12.7%), pelvis (4.9%) and ureter (3.2%) [8, 9]. Pheochromocytoma in bladder occurs between the third and fifth decade but may also occur at any age [10]. The characteristic signs and symptoms are hypertension and hematuria. Painless hematuria has been seen in 50-60% of the cases and hypertension in 65-80% cases [11, 12]. As to the primary composite pheochromocytoma in bladder, there were no statistical reports. At the present, diagnosis of composite pheochromocytoma is completely based on histopathological findings [13]. Metastatic lesions of these tumors are almost always derived from the neural component. Shawa H, et al [14] reported that pheochromocytoma-ganglioneuroma composites are indistinguishable from pheochromocytomas clinically and radiologically. Thus, they suggested that these two types of tumor could to be managed similarly. Moreover, their study stated that the age of composite pheochromocytoma ranged from 14 to 74 and the median age was 50, and patients with composite tumors tended to be older than those with pure pheochromocytomas. Their conclusions were concordant with ours. Comstock, et al [15] demonstrated that neither composite pheochromocytoma nor classic pheochromocytoma harbored N-MYC amplification. The neuroblastic elements in composite pheochromocytoma recapitulated favorable histological neuroblastoma in their pathological features, with low mitotic-karyorrhectic index and absence of N-MYC amplification and favorable outcome. Their findings also corresponded with ours. Rao [16] suggested that composite pheochromocytoma did not have adverse prognostic significance conferred by the neuroblastic elements. However, the prognosis of composite pheochromocytoma may be difficult to predict. The rate of metastasis and death appeared to be higher in cases with the second component being not ganglioneuroma [17-20]. Careful attention should be paid to the occurrence of endocrine symptoms and alteration of hormone levels during prolonged follow-up on young patients with composite pheochromocytoma [21].

Surgical resection is a preferred management. The effect of adjuvant therapy is unclear since it has not been widely adopted. Fujiwara, et al [22] reported a case of compound adrenal tumor, which was consisted of pheochromocytoma and ganglioneuroblastoma in an adult. They gave no adjuvant therapy and there was no evidence of recurrence within 5 years of follow-up. Khan, A N, et al [5] summarized the literature and concluded that treatment of composite pheochromocytoma remained the same as pheochromocytoma. For patients with functional disorder, urinary VMA and catecholamine detection are useful in diagnosis and follow-up. Moreover, measurement of urinary catecholamine level can help to monitor the recurrence and metastasis of this tumor.

In summary, composite pheochromocytoma seems to have similar clinical findings, treatment strategies and outcomes with pure pheochromocytoma, nevertheless further studies of composite pheochromocytoma are necessary to achieve a better understanding of this type of tumor.

Conclusion

Primary composite pheochromocytoma in urinary bladder is an extremely rare variant of pheochromocytoma. It has distinctive clincopathologic features. Notably, diagnosis of this entity can only be made basing on histopathologic features observed by pathologists.

Treatment of this tumor remains the same with pheochromocytoma. Surgical resection is a preferred management. Patients with localized composite pheochromocytoma have an extremely favorable prognosis. The rate of metastasis and death is higher in cases with the second component being not ganglioneuroma.

Disclosure of conflict of interest

None.

Abbreviations

MRI, magnetic resonance imaging; CT, computerized tomography; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; SYN, Synaptophysin; CGA, Chromogranin-A; NSE, neuron-specific enolase.

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