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Bladder Paraganglioma: Three Cases Report and Literature Review

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Background: Bladder paraganglioma (BPG) is one of the rare neuroendocrine neoplasms that develops from neural crest cells. It categorizes into functional and non-functional types based on the catecholamines secretion. Currently, functional BPG is predicted in advance based on signs and symptoms of catecholamine excess, such as hypertension and "micturition attacks". However, it is often overlooked because of its rareness. Misdiagnosis of a functional tumor may increase the risk of surgical intervention.

Case Presentation: We reported 3 cases of BPG that they were admitted to the hospital due to abdominal pain or gross hematuria. Computed tomography (CT) scans showed space-occupying lesions in the bladders with diameters less than 3cm. There were no typical catecholamine excess symptoms before surgical intervention. Postoperative pathology confirmed BPG after removal of the tumor. We also analyze 69 cases of BPG that has been reported and found that 78.0% cases were functional among the tumors larger than 3cm.

Conclusion: Bladder tumors larger than 3cm in diameter can serve as an additional predictor of functional BPG. Patients who are suspected should undergo magnetic resonance imaging (MRI) scans, 123/131 metaiodobenzylguanidine (MIBG) scan, and have their catecholamine levels tested. Once the diagnosis is confirmed, patients should be started on fluid replacement therapy and adrenergic blockade to abate the disorders associated with catecholamine excess.

Keywords: bladder paraganglioma, cases report

Background

Paraganglioma is one of the rare neuroendocrine neoplasms that derives from neural crest cells. BPG is extremely rare. It constitutes less than 6% of all paragangliomas and 0.06% of all primary bladder tumors.[1,2] Since Zimmerman reported the first known case of BPG in 1953,[3] the number of reported cases has accumulated only about 185.[2]

BPG can be categorized into functional and non-functional types. 61.3% of BPG cases were reported to be functional.[4] Functional tumors often manifest in catecholamine release induced by micturition. Symptoms may include paroxysmal hypertension, palpitation, headache, dizziness, sweating and even syncope.[5,6] The non-functional type is usually presented with painless gross hematuria and is indistinguishable from other types of bladder tumors. Because of its rareness, clinicians often do not consider BPG when diagnosing bladder-occupying lesions. This can lead to misdiagnosis and increase the perioperative risks and complications, especially the functional types. There has been reported that BPG without typical signs and symptoms developed malignant hypertension during surgical resection.[7–12] Therefore, preoperative identification of BPG is of great importance.

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To increase awareness and understanding of BPG, we report on three patients who were diagnosed and treated for BPG in our hospital. In addition, we analyzed all the reported cases in order to identify other factors that might improve the diagnosis of functional BPG before surgery.

Case Presentation

Three patients with BPG in our hospital were between the ages of 45 and 60. They were admitted for abdominal pain or gross hematuria without family history (Table 1). CT scans showed space-occupying lesions in the bladders with diameters less than three centimeters (Figure 1). There were not any typical catecholamine excess symptoms before surgical intervention. Intraoperative blood pressure was stable. Surgical pathology based on the immunohistochemical staining (Figure 2), which included chromogranin, synaptophysin, Vim, Ki67, S100 and cytokeratin, confirmed the diagnosis of benign BPG.[13] Bladder cancer was considered before the operation. Fortunately, it was the benign tumor and the vital signs were stable during the operation. Follow-up cystoscopy performed at three, six, and twelve months showed no recurrence.

Discussion and Conclusions

BPG is a rare tumor that currently has no single specific predictor for the preoperative diagnosis, which is easily misdiagnosed as bladder carcinomas. Preoperative misdiagnosis would pose a potential risk for the treatment. We reviewed the case reports of BPG published from 2010 to 2021 in order to find the specific predictor.[7–12,14–62] There was a total of 69 cases, including the three cases of ours. Tumors with diameters larger than 3cm were recorded in 41 cases, and less than 3cm in 28 cases. Among the tumors larger than 3cm, 78% were functional, and the smaller than 3cm only 28.6% (Figure 3). We believe that the functional BPG should be considered when the tumor is larger than 3cm.

Table 1 The Data of the Three Cases

	Case 1	**Case 2**	**Case 3**
Age (year)	45	53	58
Sex (F/M)	F	F	M
Chief complaint	Gross hematuria	Abdominal pain	Gross hematuria
Micturition syncope/ palpitations	No	No	No
Catecholamine and urine VMA after surgery	Normal	Normal	Normal
Urine cytology	No malignant cells	No malignant cells	No malignant cells
Family history	No	No	No
Bladder lesion			
Imaging	CT	CT	CT
Size (cm)	Length 2.0 Width 1.5	Length 2.3 Width 2.1	Length 2.0 Width 2.0
Location	Left wall	Anterior wall	Posterior wall
Enhancement arterial phase	Yes	Yes	Yes
Lymph metastasis	No	No	No
Surgical procedure	TURBT	TURBT	TURBT
Intraoperative blood pressure	Normal	Normal	Normal
Peri-operative	Uneventful	Uneventful	Uneventful
Immunohistochemistry			
CgA(chromogranin)	Positive	Positive	Positive
Syn(synaptophysin)	Positive	Positive	Positive
Vim	Positive	Positive	Positive
Ki67	Negative (<1%)	Negative (<1%)	Negative (<1%)
S100	Positive in sustentacular cell	Positive in sustentacular cell	Positive in sustentacular cell
CK (cytokeratin)	Negative	Negative	Negative

Figure 1 The CT scans of the three cases. (**A**) Case 1, CT scans of the tumor on the left wall of bladder. (**B**) Case 2, CT scans of the tumor on the bladder anterior wall. (**C**) Case 3, CT scans of the tumor on the posterior wall of bladder.

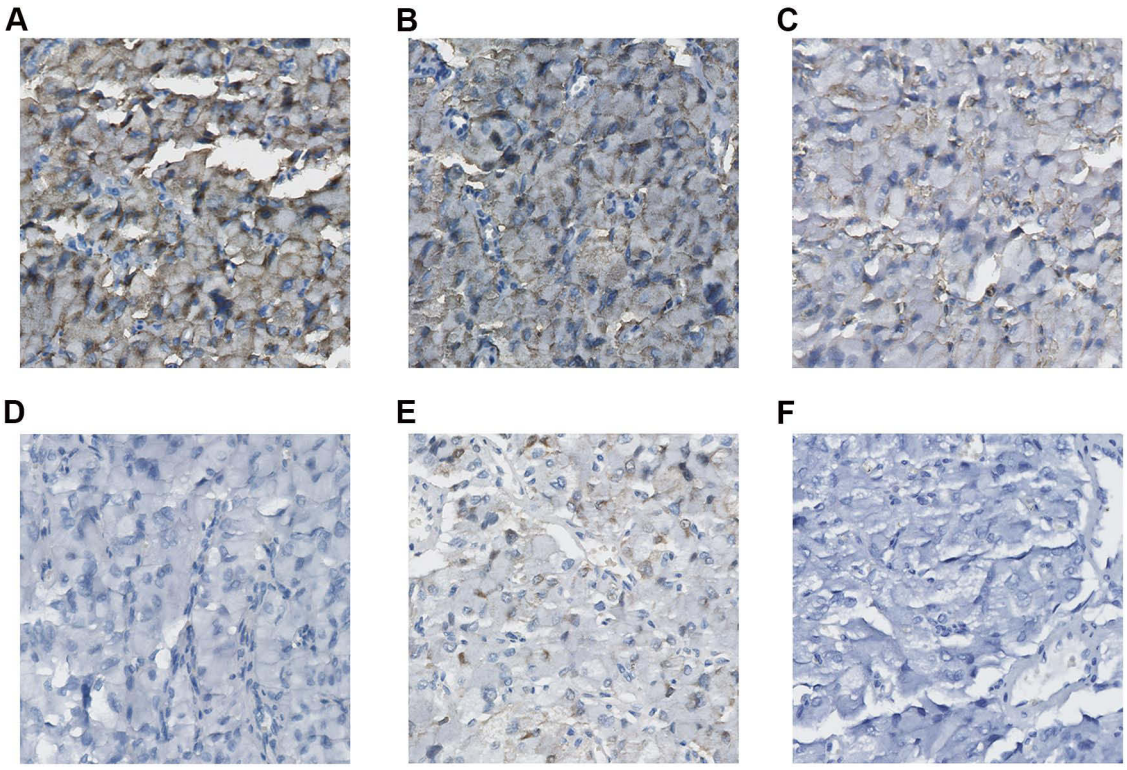

Figure 2 Immunohistochemical staining of the three cases. Immunohistochemistry. Brown staining indicates the positive result (X400). (**A**) Positive for synaptophysin. (**B**) Positive for chromogranin. (**C**) Positive for Vim. (**D**) Negative for Ki67. (**E**) The sustentacular cells are stained positive for S100 protein. (**F**) Negative for cytokeratin.

In addition, there have been suggesting that preoperative diagnosis can be inferred from imaging and blood indicators. Wang et al found that an intensely enhanced round or oval-shaped bladder lesion on T1 weighted images are a key MRI feature for paraganglioma.[63] On the T2 weighted images, the paraganglioma may exhibit a hyper-intense "salt and pepper" appearance that can differentiate it from other bladder tumors.[64] Liang et al reported that bladder masses that display strong hyperintensity on diffusion-weighted MRI images may also be a characteristic of BPG.[65] However, MRI cannot distinguish whether the tumor is functional. 123/131MIBG scan, an isotope-imaging technique, has been applied to detect the catecholamine-secreting tumor. The sensitivity for the paraganglioma is 77~99% and the specificity is 95~100%. But the sensitivity decreases in cases of extra adrenal paragangliomas, metastatic paragangliomas, and recurrences.[66]

Paraganglioma is a neuroendocrine neoplasm that secretes catecholamines. Functional BPG may present with elevated levels of catecholamines, especially during micturition. This phenomenon is referred to as "micturition attacks"[67,68] and is usually manifested by

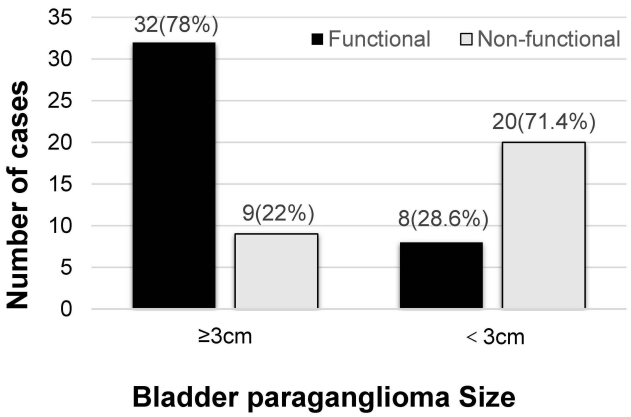

Figure 3 The Bladder paraganglioma size. Proportion of functional and non-functional BPG larger than 3 cm or smaller than 3 cm in diameter.

headache, palpitations, and syncope. However, 10% of functional tumors may exhibit only minimal or non-specific symptoms,[69] which is so dangerous. Seven cases of above did not present typical clinical symptoms, but the blood pressure both rose higher than 200mmHg during operation.

Priyadarshi et al reported that the BPG is most commonly situated at the dome or the trigone of the bladder. Nevertheless, our study found that it is mostly located in the sidewalls (Figure 4). Musa Male et al compared the characteristics of BPG and urothelial carcinomas using cystoscopy, and found that NPB is more likely to manifest as vascular proliferation, but less likely to have bleeding, necrosis, calcification, pedicles, and multiple lesions.

Surgical resection remains the mainstay treatment for BPG. Some reports suggest that partial cystectomy is the better treatment option.[70] Others recommended transurethral resection of bladder tumor (TURBT).[71] We suggest the tumor less than 3cm can be removed through TURBT, depending on the pathology to decide whether further surgical treatment is required. For those larger than 3cm or invaded the full bladder wall, partial or radical cystectomy should be considered. Regardless of the surgical method, preoperative adrenergic blockade to stabilize blood pressure and fluid replacement therapy are recommended for functional tumors.

BPG is a rare bladder tumor that is often missed by clinicians. It can be predicted based on micturition attacks and/or signs and symptoms of catecholamine excess. We suggest that bladder tumors larger than 3cm in diameter can be used as an additional predictor of functional BPG. Patients who are suspected to have functional BPG should undergo MRI scan, 123/131 MIBG scan, and have their catecholamine levels tested. Once a functional tumor is confirmed, patients should be initiated on fluid replacement therapy and adrenergic blockade to abate the disorders associated with catecholamine excess.

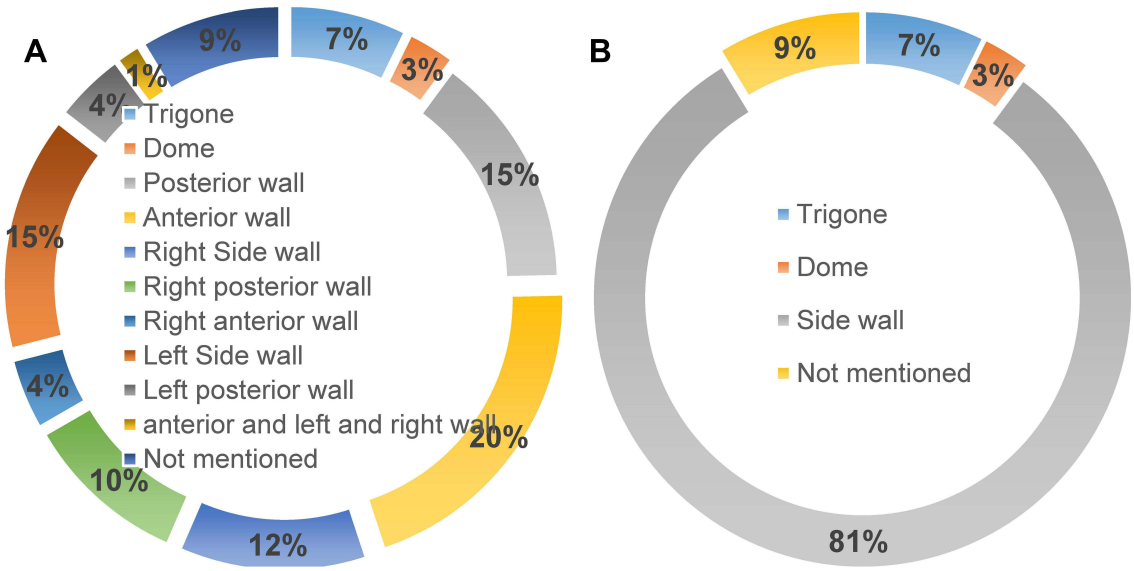

Figure 4 The distribution of the BPG. (**A**) Distribution proportion of different parts. (**B**) Side wall proportion.

Data Sharing Statement

The datasets analysis during the current study are available from the corresponding author on reasonable request.

Consent for Publication

Written informed consent to publish was obtained from all three patients reported.

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Disclosure

The authors declare that they have no competing interests.

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