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Case Report

A rare case report: vaginal paraganglioma

Leilei Fan*, Liguo Ma*

*Department of Gynecology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen 518020, Guangdong, China. *Equal contributors and co-first authors.*

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Abstract: Vaginal paraganglioma (VP), usually solitary and primary, is a rare adrenal type paraganglioma derived from the anterior neural crest, and can be classified as a functional or non-functional tumor. Only 10 cases of VP have been reported since 1955. Herein, we report an unusual case of a 39-year-old female VP patient with symptoms of hypercatecholaminism and a family history of hypertension. After preoperative control of blood pressure with an alpha-receptor blocker, laparoscopic surgery was performed. The blood pressure fluctuated after touching the tumor intraoperatively, and the tumor was successfully and completely removed under anesthesia by surgery. Postoperative pathology confirmed the diagnosis. The clinical characteristics, auxiliary examination, morphological and pathological immunohistochemical characteristics, and perioperative treatment of VP are analyzed, and the literature of the previous 10 cases is reviewed, so as to help further understand VP and provide clinical guidance.

Keywords: Paraganglioma, vagina, immunohistochemistry, metastatic potential

Introduction

Paraganglioma is a rare extra-adrenal neuroendocrine tumor derived from neural crest precursors, that can be classified into functional and non-functional tumors. Such tumors rarely occur in the female genital tract. Vaginal paraganglioma (VP) is an extremely rare tumor, and is usually a solitary primary paraganglioma. We report a case of functional VP treated by laparoscopic surgery, and review the literature of previous cases of VP, so as to gain a deeper understanding of VP and provide guidance for future diagnosis and treatment.

Case data

A female patient aged 39 years had four pregnancies and two deliveries with normal menstruation, and the deliveries were in 2009 and 2016 by cesarean section. She was admitted to Shenzhen People's Hospital on August 24, 2018 with the complaints of headache, palpitation, and elevated blood pressure for 7 years. The symptoms were paroxysmal and pulsatile headache with dizziness, sweating and nausea, lasting about 5-6 minutes each time, and could be relieved after rest. The symptoms occurred once or twice a month, and did not occur during sexual intercourse. The measured blood pressure fluctuated between 160-190/100-110 mmHg, with no inducement prior to seizure. Primary hypertension was diagnosed, and the treatment with Nifedipine Controlled-Release Tablets showed unsatisfactory results and recurrent episodes.

She had a natural pregnancy in 2016. The blood pressure tended to elevate episodically in the first and second trimesters, reaching a maximum of 220/125 mmHg. The aforementioned symptoms began to occur once a day. Oral antihypertensive drugs (Methyldopa + Labetalol) were given, but the efficacy was unsatisfactory. Gestational diabetes mellitus was diagnosed at the 24th week of gestation, and insulin hypoglycemic therapy was administered. At the 34th week of gestation, the pregnancy was terminated by cesarean section due to "severe preeclampsia", and the delivery went smooth. Oral antihypertensive drugs were continuously taken after delivery, and the blood pressure fluctuated between 200-220/100-110 mmHg. The oral

glucose tolerance test result was abnormal at 42 days after delivery. Blood and urine tests at 3 months after delivery suggested a pheochromocytoma. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) suggested that a soft tissue mass with elevated metabolic activity between the left posterior wall of the bladder and the left side of cervix was about 6.02 × 3.88 × 3.68 cm in size, and its density was slightly lower than that of uterine parenchyma. The mass was closely related to the left posterior wall of bladder, and was unclearly bounded by the adjacent cervix. The left anterior wall of the rectum was slightly compressed, and no lesions were observed in adrenal glands. Subsequently, the antihypertensive drugs (Valsartan + Doxazosin) were given, but the efficacy was unsatisfactory. She was later admitted to hospital with "suspected paraganglioma". Her grandmother and uncle had a history of "hypertension". At admission, she received gynecological examinationshowing marital outlet; unobstructed vagina and no abnormal secretions were observed; the left, middle and upper portions of vagina bulged up (about 4 × 4 cm) to the left vaginal fornix, and the appearance of vaginal mucosa was normal. The bimanual examination showed an accessible medium-hard mass (about 6 × 5 × 4 cm in size) in the left upper vagina, and the mass was closely related to the vaginal wall, with a clear boundary, moderate activity, and no tenderness. The mass protruded to the left rear of bladder and was closely related to the paracervical tissue and the left ureteral tunnel, and there was a cleft between the mass and the cervix. The uterine body was located in the anterior position, often large and medium-hard, with a smooth surface and good activity, and no tenderness. No obvious abnormality was observed in the two adnexa, and no tenderness was observed. The vanillylmandelic acid test showed 15.13↑ mg/24 h (normal value < 13.6 mg/24 h). The serum metanephrine test suggested 0.12 mol/L (normal value ≤ 0.5 mol/L). The serum methoxyepinephrine test revealed 13.95↑ nmol/L (normal value ≤ 0.9 nmol/L). The blood-fasting sugar test exhibited 7.16↑ mmol/L. The glycosylated hemoglobin test showed 6.5%. The electrolyte and aldosterone tests of erect position and 24-h urocortisol test showed normal results. An informed consent was signed by the patient. After admission, she was administered with 10 mg of phenoxybenzamine po bid, and the blood pressure fluctuated between 125-140/88-96 mmHg. VP was diagnosed preoperatively. The patient underwent laparoscopic resection of paraganglioma from the vaginal wall under general anesthesia on September 28, 2018. The preoperative blood pressure was 100/70 mmHg, and the heart rate was 50 beats/min. During the surgery, the tumor was found to originate from the left lateral wall of vagina, and the tissue space between the tumor and the left posterior wall of bladder was dense, with a size of about 6 × 4.5 × 4 cm. There was an adequate blood supply. After intraoperative touch of the tumor, the blood pressure fluctuated significantly, with a maximum blood pressure of 210/120 mmHg and a maximum heart rate of 110 beats/min. After complete resection of the tumor, total encapsulation was observed. The postoperative blood pressure was 110/70 mmHg, and the heart rate was 80 beats/min. The tumor on sectioning was grayish yellow with soft texture, with hemorrhage and necrosis as the focal lesions (**Figure 1A**, **1B**).

Postoperative pathology revealed that the pelvic tumor was located in the muscular layer, and was arranged in a "zellballen" shape. The mesenchyme was rich in thin-walled blood vessels, and some nests were enlarged (at least 3 times larger than those of peripheral cell nests). The neoplastic cells were round and polygonal, with unclear cell boundaries. The cytoplasm was eosinophilic, basophilicc, or amphophilic, and partially transparent, with obvious nucleoli in some regions. There were 1-5/10 HPF abnormal mitotic figures. Necrosis was observed locally, and infiltrative growth was observed in some regions, around which a small amount of vaginal wall tissue was observed. According to immunohistochemical expression, the lesion was suspected as paraganglioma with malignant potential. Immunohistochemistry (IHC): CK (-), CgA (+), Syn (+), CD56 (+), S-100 staining for cells+ (reduced or missing cells could be stained in some regions), and Ki-67 (about 5%+). Special staining: the reticulin staining suggested enlarged nests of tumor cells (**Figure 1C-F**) and **Figure 2A-F**. Pheochromocytoma/paraganglioma gene test: the succinate dehydrogenase subunit B (SDHB) gene mutation was detected (NM_003000: c.343C > T (p.

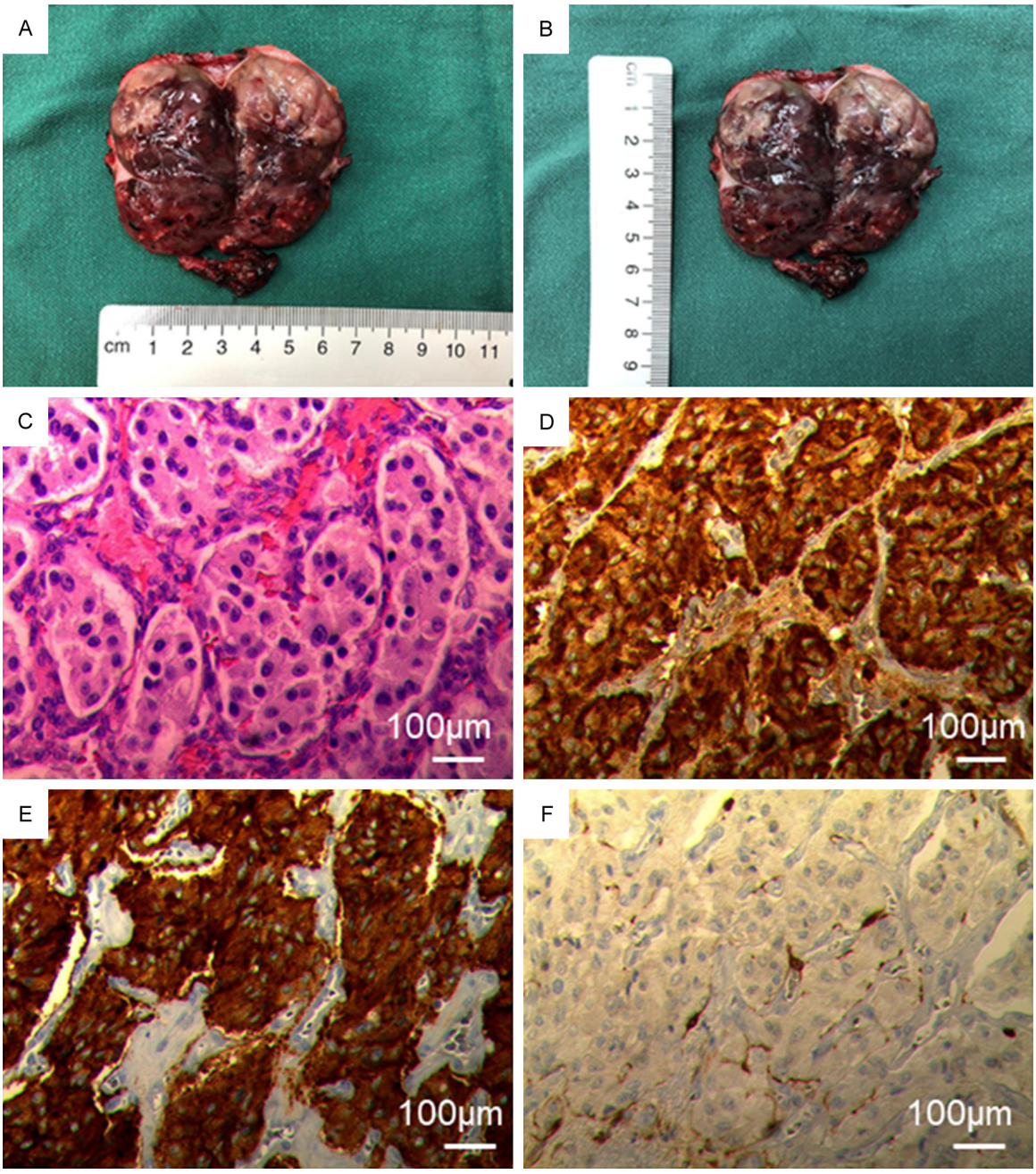

Figure 1. Surgical resection specimen of vaginal paraganglioma and special staining images. A, B: Surgical resection specimen; C: Cells are arranged like "zellballen"; D: Chromogranin A was diffusely positive; E: Synaptophysin was diffusely positive; F: S-100 staining for cells+.

R115*) Guangzhou Kingmed Center for Clinical Laboratory).

On the 11th day after the surgery, the patient was discharged, with healed vaginal wound II/Class A, no more symptoms (e.g., headache, palpitation and cold sweat), and normal levels of blood pressure (110-120/70-85 mmHg) and blood glucose (fasting blood sugar < 5.2 mmol/L). Postoperative follow-up showed no discomfort (**Figure 3**).

Discussion

Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare, heterogeneous neuroen-

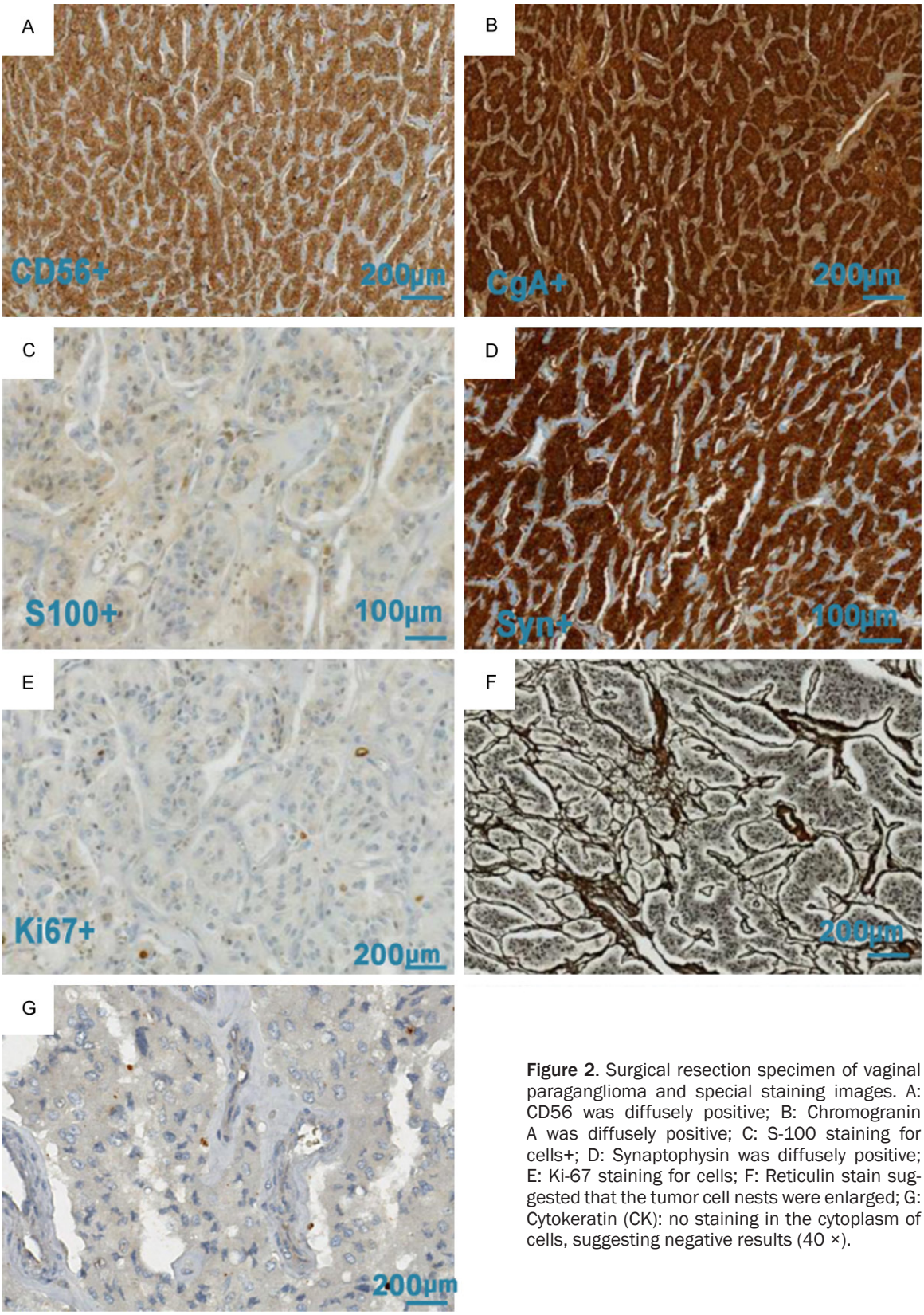

Figure 2. Surgical resection specimen of vaginal paraganglioma and special staining images. A: CD56 was diffusely positive; B: Chromogranin A was diffusely positive; C: S-100 staining for cells+; D: Synaptophysin was diffusely positive; E: Ki-67 staining for cells; F: Reticulin stain suggested that the tumor cell nests were enlarged; G: Cytokeratin (CK): no staining in the cytoplasm of cells, suggesting negative results (40 ×).

docrine neoplasms of the autonomous nervous system of chromaffin cell origin. PCCs, adrenal sympathetic paragangliomas, only arise from chromaffin cells in the adrenal medulla. PGLs

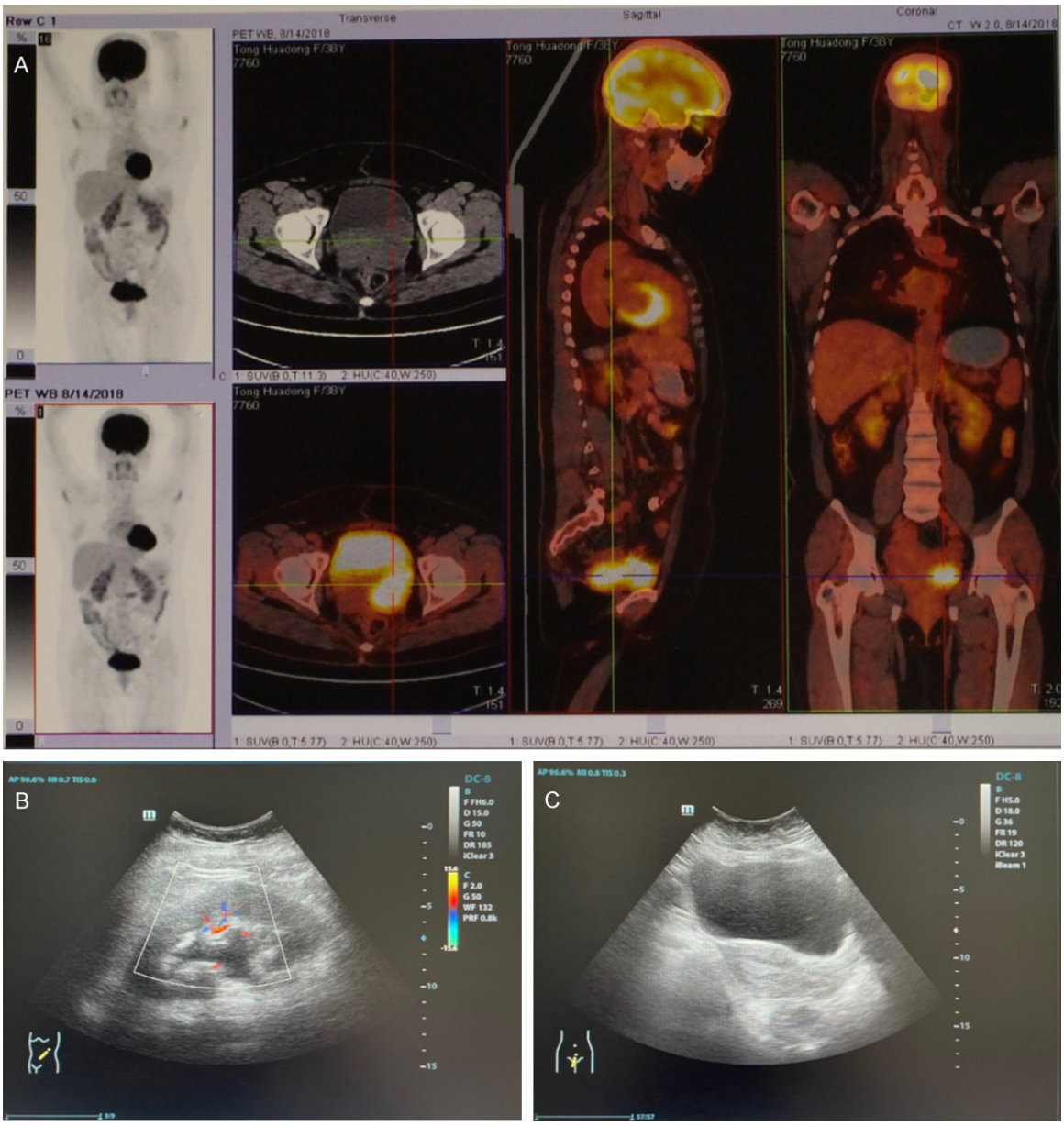

Figure 3. Related imaging data of the patient before and after treatment. A: PET-CT image before treatment; B: Urologic color ultrasound after 1-month treatment; C: Color doppler ultrasonography of uterine adnexa after 1-month treatment.

are a non-epithelial tumor derived from extra-adrenal chromaffin cells originating from neural crest-derived paraganglion cells, and are located in the sympathetic or parasympathetic paraganglia region [1]. PCCs and PGLs are commonly denoted as pheochromocytomas and paragangliomas (PPGLs). Parasympathetic PGLs include carotid body tumors and usually non-functional tumors involving the paraganglia along the cervical and thoracic branches of the vagal and glossopharyngeal nerves. Sympathetic PGLs include tumors arising from the aortic bodies, paravertebral sympathetic chains (cervical, thoracic and abdominal), and sympathetic nerve fibers in the pelvic and retroperitoneal organs, which usually secrete catecholamine [2]. Therefore, the clinical manifestations are asymptomatic, hypercatecholaminemia and lump-induced pressure symptoms. Hypercatecholaminism is characterized by paroxysmal or persistent hypertension and metabolic disorder. Paroxysmal or per-

sistent hypertension may occur without triggers and may be induced by agitation, posture changes, smoking, urination and defecation. During the attack, patients experience palpitation and tachycardia accompanied by severe headache, anxiety, tremors in limbs or head, paleness, sweating, hypothermia, numbness, and sometimes shortness of breath, chest distress, and dyspnea accompanied by nausea, vomiting, and middle and upper abdominal pain from time to time. In some patients (particularly pediatric/teen patients), the disease progresses rapidly and is characterized by accelerated hypertension, severe damage to the fundus, short-term optic atrophy that leads to blindness, azotemia, cardiac insufficiency and hypertensive encephalopathy. A few patients may have paroxysmal hypotension, even shock or alternate between hypertension and hypotension. As for metabolic disorder, nearly half of the patients have symptoms similar to hyperthyroidism. The expedited decomposition of liver glycogen and the inhibition of insulin secretion can lead to elevated blood glucose level and impaired carbohydrate tolerance, resulting in secondary diabetes mellitus.

Table 1 shows that only 10 cases of VP have been reported globally since 1955 [3-12]. Of the 10 patients, 5 developed hypercatecholaminism, and 2 had no clinical VP symptoms and normal blood pressure, and only a vaginal mass was identified by physical examination. Due to the special site of VP, 6 patients had symptoms (such as irregular vaginal bleeding, massive vaginal bleeding, and pruritus of vulva induced by increased vaginal secretions). In our case, paroxysmal hypertension and secondary diabetes mellitus occurred, which was consistent with the clinical manifestations of functional sympathetic paraganglioma.

With functional paraganglioma, the secretion levels of catecholamine and noradrenaline in the blood and urine were noticeably elevated (as shown in this case). It is widely believed that the objective of biochemical tests is to detect catecholamine metabolites (methoxytyramine, normetanaephrine and 3-metanephrines) rather than catecholamine itself (dopamine, noradrenaline, and epinephrine) [13]. However, these biomarkers are not yet routinely tested by most medical institutions. In terms of imaging, the extensively implemented tests (e.g., B-mode ultrasound, CT, and MRI) can only be used for the location of paraganglioma. ^{18}F-FDG PET-CT and ^{18}F-DOPA PET/CT are implemented for the diagnosis of primary, multifocal, and metastatic paraganglioma. In this case, ^{18}F-FDG PET-CT indicated an abnormal increase in fluorodeoxyglucose (FDG) metabolism in the tumor. Recent evidence has demonstrated that ^{68}Ga-DOTATATE PET/CT is superior to ^{18}F-FDG PET-CT and ^{18}F-DOPA PET/CT in performance [14]. ^{123}I-MIBG is a radioactive labeled molecule similar to noradrenaline, which is conducive to positioning and diagnosis of tumors.

Previously, only 50% of patients with VP were reported to have hypercatecholaminism, and the tumors were 1.4-6.0 cm in size and varied in shape. Additionally, non-functional tumors were often confused with vaginal rhabdomyosarcoma, hemangiopericytoma and vaginal wall cysts. Therefore, pathology and IHC tests remain the gold standard for diagnosis of tumors. The vascular matrix contains large amounts of granular cytoplasm that is amphophilic, eosinophilic, or basophilic. There may be neoplasms with nuclear atypia, but mitosis and necrosis are rarely observed. Immunostaining showed that chromogranin A (CgA), Synaptophysin (Syn) and S-100 were positive, and CgA and Syn staining were observed in the cytoplasm of tumor cells, while S-100 staining provided a special strong positive staining, highlighting the supporting cells in the tumors. According to the previous 10 case reports, the pathological and immunohistochemical results were basically consistent with the aforementioned results. However, CgA and Syn staining were positive in all types of non-epithelial neuroendocrine tumors, and S-100-positive supporting cells also appeared in various sites of epithelial neuroendocrine tumors. In non-epithelial neuroendocrine tumors, the paraganglioma keratin was generally deficient, and this could be used as an important marker for differentiation of epithelial neuroendocrine tumors. Pan-keratin antibodies (e.g., AE1/AE3 and CAM 5.2 antibodies) are strongly positive in epithelial neuroendocrine tumors, and thus are recommended as markers [15]. In this case, staining showed negative for CK (cytokeratin, AE1/AE3), further confirming the diagnosis. None of the previous 10 case reports sug-

Table 1. Characteristics of 10 cases of vaginal paraganglioma

Author	Year	Age	Location	size (cm)	Symptoms	Treatment	Follow-up (months)
Plate [3]	1955	66	posterior vaginal wall	walnut size	vaginal bleeding	Surgical resection	Not reported
Pezeshkpou [4]	1981	22	anterior vaginal wall	3 cm × 2.5 cm × 1.5 cm	asymptomatic	Surgical resection	Not reported
Parkes *et al*. [6]	1998	11	Not reported	5 cm	vaginal bleeding	Surgical resection	Not reported
Hassan *et al.* [7]	2003	24	left posterior wall of vaginal fornix	2.5 cm	hypertension, tachycardia, heart failure	Surgical resection	4
Brustmann *et al.* [8]	2007	33	right vaginal wall	1.9 cm and 1.4 cm	vaginal bleeding	Surgical resection	lost to follow up
Shen *et al.* [10]	2008	38	anterior vaginal wall	3.0 cm	Paroxysmal headache, chest tightness, palpitations	Surgical resection	36
Akl *et al.* [11]	2010	65	top wall of vagina	2.5 cm × 2.3 cm × 2.0 cm	asymptomatic	Surgical resection after arterial embolization	Not reported
Cai *et al.* [12]	2014	17	right vaginal wall	3.5 cm × 3.0 cm × 2.5 cm	vaginal bleeding	Surgical resection	12
Sharma *et al.* [20]	2018	28	left vaginal wall	3 cm × 3 cm	asymptomatic	Surgical resection	Not reported
Wong *et al.* [21]	2020	15	left anterior vaginal wall	3 cm	Menorrhagia, dysmenorrhea and anemia	Surgical resection	56

gested that the tumor was non-benign. In this case, there were 1-5/10 HPF pathological mitotic figures, local necrosis was observed, and infiltrative growth was observed in some regions. Ki-67 staining rate was about 5%+, suggesting malignant potential.

Thirty percent of paragangliomas are genetic tumors and are hereditary. To date, more than 20 spontaneous or hereditary gene mutations have been found to be related to their occurrence, and SDHB is primarily observed in sympathetic paraganglia. The American Society of Clinical Oncology recommends that all patients with PPGLs should undergo genetic screening [16]. Up to 45% of patients with PPGLs have germline mutations in known predisposing genes. Since such mutations are associated with other malignancies, the identification of these mutations has important clinical implications. Early diagnosis and treatment can be achieved through genetic tests. Based on clinical data, such as positive family history, age, and history of hypertension, it is easier to identify the types of genes involved. For example, hypertension is more common in patients with multiple endocrine neoplasia type 2 (MEN2) (60%) than in patients with von Hippel-Lindau (30%). Pediatric or teen patients with PGLs should first undergo SDHB mutation testing. Elevated noradrenaline is common in von Hippel-Lindau, and increased epinephrine is common in MEN2 [17].

Surgical resection was reported in all VP cases. Only 1 case underwent partial resection, yet I-MIBG scan was negative after surgery, and repeated biopsies showed only reactive tissues. In all other cases, the tumor was completely resected, and their blood pressure returned to normal after surgery. No relapse was observed after 3 months to 3 years of follow-up. Therefore, surgical treatment currently remains the most effective option. In addition, since functional paraganglioma can lead to hypertensive crisis or even life-threatening events during surgery, and some functional paragangliomas are in dormancy before surgery, perioperative management plays a pivotal role, so a thorough assessment should be performed preoperatively. In the case of hypercatecholaminism, α-receptor blockers are often used to suppress the release of catecholamine. Based on the location of vaginal tumors and the blood supply, preoperative interventional embolization of uterine artery should be performed (in one reported case). An anesthetist should be in place to comprehensively evaluate the patient's conditions before surgery, and closely monitor and manage the intraoperative anesthesia. Our case was treated with phenoxybenzamine preoperatively, and stable blood pressure was maintained. After intraoperative manipulation of the tumor, the blood pressure was elevated. The surgery was successfully completed after timely treatment by an experienced anesthetist to maintain a stable blood pressure.

At present, there are no histological criteria available for the evaluation of the biological behaviors of PPGLs. In 2017, World Health Organization canceled the classification of benign and malignant tumors, and changed the diagnosis of "malignant" to "metastatic" based on the consideration that all tumors have the potential for metastasis. It is believed that the large tumor size, sites of extra-adrenal tumors, catecholamine spectrum, and SDHB mutation status are important risk factors for metastatic behaviors [18]. A large-scale meta-analysis indicated that the 5-year survival rate of patients with metastatic PPGLs was 63% [19]. Currently, the literature does not suggest relapse of VP because of short-term follow-ups. Therefore, patients with VP should receive lifelong follow-ups in view of the metastatic potential of VP.

In conclusion, given the metastatic potential of VP, follow-ups for life are recommended in VP patients to observe for relapse. This provides guidance for future clinical work.

Disclosure of conflict of interest

None.

Address correspondence to: Liguo Ma, Department of Gynecology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), No. 1017, Dongmen North Road, Luohu District, Shenzhen 518020, Guangdong, China. Tel: +86-13724380898; E-mail: fanleilei2568@163.com

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