

Case Report

Paraganglioma of the vulva: a case report and review of the literatures

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Abstract: Vulva paragangliomas are rare and usually misdiagnosed or missed diagnosed, especially those come from juvenile. We described a functional paraganglioma derived from vulva, which was misdiagnosed with clear cell carcinoma, and the vaginal wall was invaded by this mass. The patient was a 17-year-old Chinese girl. The tumor was surgical removed smoothly. The girl has been followed-up for eighteen months without any evidence of recurrence and metastasis up to now. Details of the patient and related articles are discussed in this report.

Keywords: Valval paraganglioma, functional tumor, diagnosis, treatment

Introduction

Paragangliomas are neuroendocrine tumors that stem from paraganglions. Paragangliomas are mostly distributed in paraganglion-gathering areas, such as the adrenal glands, neck, mediastinum, and retroperitoneum, but they rarely occur in the vaginal wall and vulva. They are even rarer in juveniles. Paragangliomas are also divided into functional and nonfunctional paragangliomas based on whether they secrete catecholamine or not and on the production of various hormones. According to previous reports, there have been only 2 cases of paraganglioma of the vulva and 8 cases of vaginal paraganglioma since 1955 [1-10]. Herein, we reported a vulval functional paraganglioma, which came from one 17-year-old girl. In particular, this tumor was misdiagnosed with clear cell cancer by fine needle aspiration biopsy (FNAC) in other hospital. The largest diameter of any previous reported paraganglioma of the vagina or vulva was 3.5 cm, making the current case, the largest functional paraganglioma of the vagina ever reported [10].

Case

The patient was a 17-year-old Chinese girl with regular menstrual periods and no history of marriage or sexual activity. The girl noticed a

hard lump located on the right side of her vulva about 2 years before seeking medical treatment. This lump was immobile, solid, and involved no bleeding. She came to a local hospital with a complaint that the lump was progressively increasing in size and a feeling of mild pain after mild physical activity. FNAC of the mass performed in county-level hospital revealed clear cell carcinoma. She was admitted to Qilu Hospital of Shandong University for operative treatment. After transferred to department of obstetrics and gynecology in Qilu Hospital of Shandong University, upon gynecologic examination, a hard mass was found on the inferior margin of the right labia minora and the lateral margin of the hymen. Digital rectal examination (DRE) showed this mass to be closely associated with the vaginal wall and rectal wall (**Figure 1**). A magnetic resonance imaging (MRI) scan of the pelvis with intravenous contrast was performed, revealing a mass on the right vulva measuring 6.0 cm*5.5 cm*4.3 cm in size, involving right levator ani muscle. In addition, the tumor invaded the vaginal wall and disrupted the continuity of its mucous (**Figure 2**).

However, inpatient evaluation revealed a blood pressure of 140-170/100-120 mmHg and a pulse rate of 90-120 beats/minute. These issues were not relieved by both metoprolol

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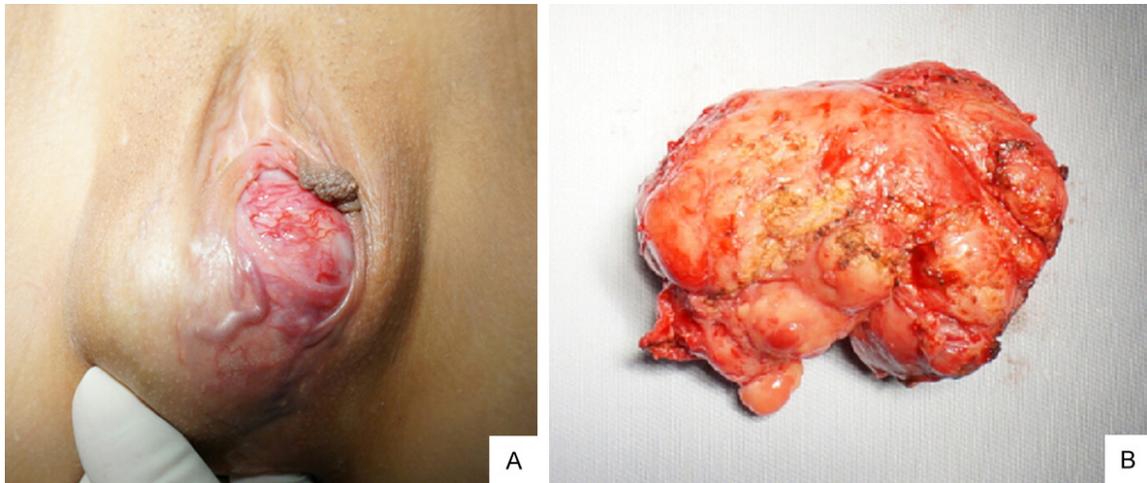
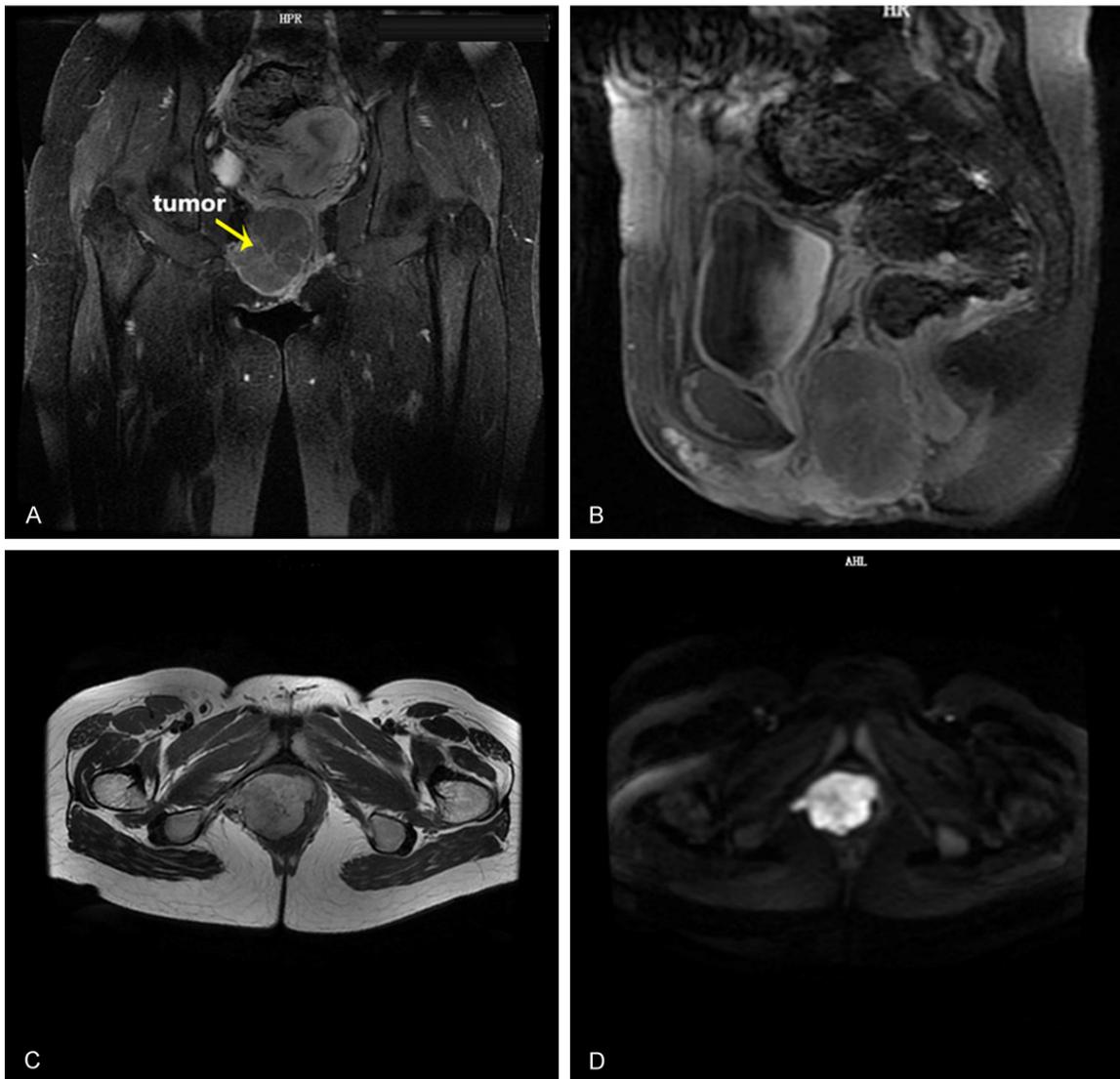


Figure 1. A: The tumor was found to be located below the right labia majora and its surface was covered with massive, engorged blood vessels. B: The isolated tumor: it was irregular ovoid in shape, tough and solid, and 7.0 cm*4.5 cm in size.



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Figure 2. Magnetic resonance imaging (MRI) scans. It revealed a mass on the right vulva measuring 6.0 cm*5.5 cm*4.3 cm in size, involving right levator ani muscle. And the tumor invaded the vaginal wall and disrupted the continuity of its mucous.

Table 1. Urinary catecholamine concentration

Term	Test Method	Result	Unit	Hint	Reference Value
Adrenaline	Radioimmunoassay (RIA)	5.46	Pg/mL		0.00-20.00
Noradrenaline	Radioimmunoassay (RIA)	>450	Pg/mL	↑	0.00-90.00
Dopamine	Radioimmunoassay (RIA)	273.11	Pg/mL		0.00-600.00

Table 2. Plasma catecholamine concentration

Term	Test Method	Result	Unit	Hint	Reference Value
Adrenaline	Radioimmunoassay (RIA)	40.23	Pg/mL		0.00-100.00
Noradrenaline	Radioimmunoassay (RIA)	3747.16	Pg/mL	↑	0.00-600.00
Dopamine	Radioimmunoassay (RIA)	167.85	Pg/mL	↑	0.00-100.00

prolonged-release tablets and nifedipine tablet. Computed tomography (CT) scanning of the enterocoelia, blood routine, serum biochemical level, female tumor markers (e.g. CA-125, CA-199, CA-724, CEA, AFP), APR (aldosterone/plasma renin activity), plasma cortisol assay, thyroid function, chest X-ray irradiation, echocardiography, and lower extremity venous ultrasound were normal.

We suspected that this vulva mass was endocrine tumor or there was some endocrine tumors not discovered in her body. The samples taken using FNAC were examined by experts from the Pathology Department and the Hematology Department of Shandong University's Qilu Hospital. These experts stated that this was not a case of clear cell carcinoma, but they did not make a definite diagnosis. In order to make a clear diagnosis and determine suitable care plan, the patient underwent biopsy after multidisciplinary joint consultation (Department of General Surgery, Department of Urology, and Department of Endocrinology), and confirmed that the growth was paraganglioma. At the same time, the patient's plasma and urinary catecholamine concentrations were measured and found to be significantly higher than normal (**Tables 1** and **2**). Further questioning regarding the patient's history found that she had suffered from severe headaches, palpitations, sweating, and pallor after intense physical activity, such as sports and physical labor, for about 2 years. These symptoms were especially common after activities

involving local compression (e.g. cycling and defecation). They had nothing to do with the patient's menstrual cycle and could be relieved by rest. After comprehensive analysis of the original material (including clinical manifestations, imaging examinations, and urinary assays of catecholamine), the diagnosis of clear cell carcinoma was revised to a diagnosis of functional paraganglioma. Computed tomography (CT) scanning of the enterocoelia was carried out to rule out tumor tissues in other parts of the body.

After oral administration of metoprolol prolonged-release tablets, nifedipine tablets, and phenoxybenzamine for 14 days and intravenous fluids for 5 days, effective circulating blood volume improved: blood pressure was 120-130/80-90 mmHg; heart rate (HR) was 90-100 beats/min; appearing symptom of stuffy nose and nail beds changed color from pale to pink. Tumor resection was performed under general anesthesia. During the operation, the tumor was found to be located below the right labia majora and its surface was covered with massive and engorged blood vessels. The right posterior lateral vaginal mucosa was involved. The tumor was removed under general anesthesia. At the exact moment that the surgeon touched the tumor during the operation, the patient's arterial blood pressure and heart rate increased dramatically to 203/132 mmHg and 114 beats/min, respectively. However, she suffered from severe hypotension (40/30 mmHg) after complete tumor excision.

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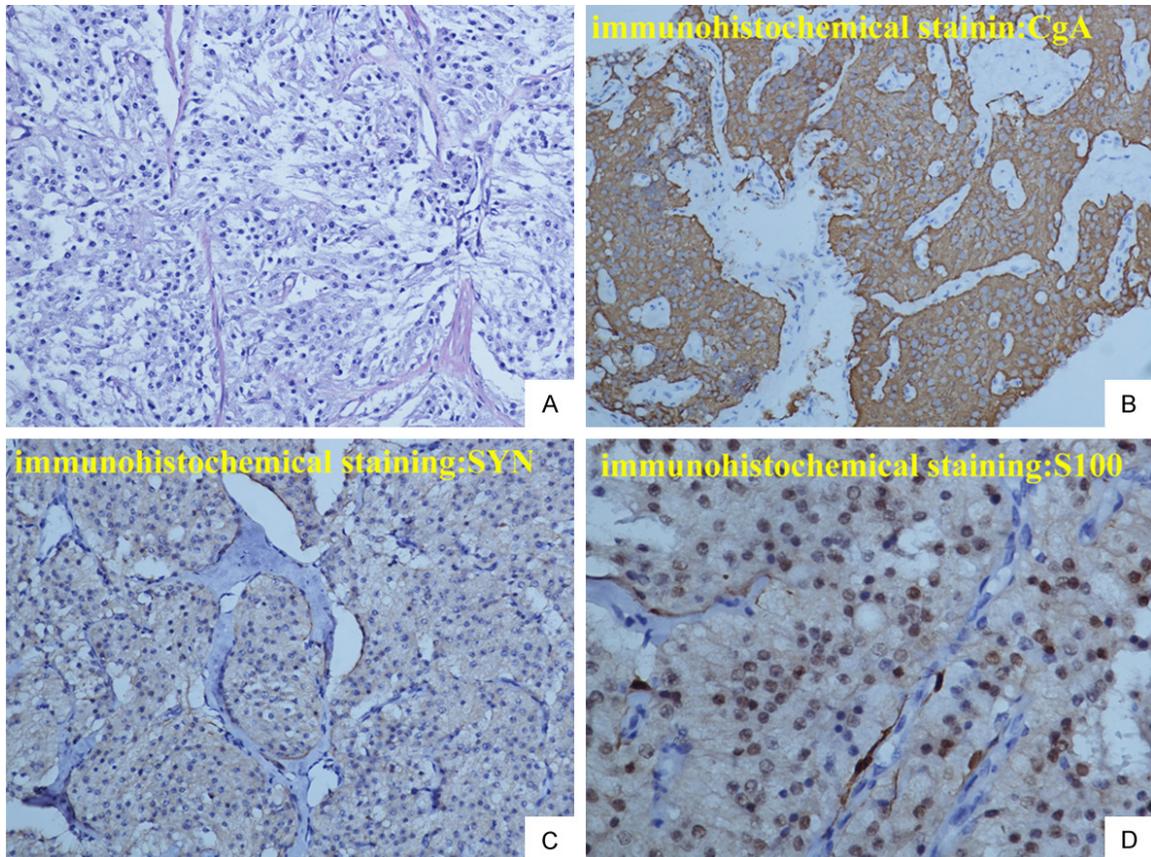


Figure 3. Immunohistochemical staining: A: The tumor cells were composed of chief cells and sustentacular cells, and they were clustered in small nests, here called zellballen, demarcated by delicate fibrous stroma and capillaries. B: Immunohistochemical staining CgA(+); C: Immunohistochemical staining SYN(+); D: Immunohistochemical staining S-100(-).

This was managed by blood transfusion and vasopressor until her vital signs became stable.

The mass removed was an irregular ovoid in shape, tough and solid, and 7.0 cm × 4.5 cm in size. The cut plane was gray-white and lobulated. An uninvolved margin of at least 5 mm surrounded the neoplasm. Microscopically, the tumor cells were composed of chief cells and sustentacular cells, and they were clustered in small nests, here called zellballen, demarcated by delicate fibrous stroma and capillaries. An immunohistochemical assay was performed, and the tumor was found to be positive for synaptophysin, chromogranin A, and desmin, but negative for protein S-100, human melanoma associated antigen, MelanA, cytokeratin, CD10, CD68, CD31, and PAX-8 (**Figure 3**). After surgery, blood pressure and heart rate were 100-110/60-70 mmHg and 90-100 beats/min, and the patient showed no manifestations sugges-

tive of catecholamine release. Another round of computed tomography of the patient's pelvic and abdominal area did not reveal any local recurrence or distant metastasis at any point in the eighteen months follow-up period, and plasma catecholamine levels remained normal.

Discussion

Paraganglioma can include both sympathetic and parasympathetic paragangliomas [11]. About 10% of paragangliomas are associated with hereditary syndromes. They are rarely reported along the genital tract, which includes the uterus, ovary, broad ligaments, vagina, and cervix [12, 13]. There have been only two reported cases of juvenile vaginal paraganglioma, one in an 11-year-old and another in a 17-year-old [5, 10]. The latter involved a functional tumor [10].

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Clinical manifestations of paraganglioma are associated with unregulated secretion of catecholamine and with the location of the tumor. Excessive secretion of catecholamine by functional tumors is largely responsible for paroxysmal or persistent hypertension and with symptoms such as palpitations, headaches, and hyperhidrosis. It can even lead to the lethal cardiovascular complications, including shock and hypertensive crisis, that classically characterize these tumors [14]. All these symptoms of oversecretion of catecholamine are usually evoked by sexual activity, childbirth, biopsy, or surgery. There have been only 3 cases of functional tumors among vaginal and vulval paragangliomas reported since 1955 [6, 8, 10]. The 2 reported patients with vaginal paraganglioma suffered from a cascade of events, including acute pulmonary edema, hypertensive crisis, severe headaches, and other symptoms, after an attempted biopsy or excision of the mass [6, 10]. Another functional case reported a 16-year history of intermittent strong paroxysmal headaches, palpitations, and chest distress. A similar episode took place during the operation [8] that was performed in attempt to remove her tumor. For these reasons, any manipulation of the tumor must be gentle, as brief as possible, and must not involve extrudation the tumor. This may prevent the release of catecholamine.

Manifestations such as those experienced by the current patient, which suggest over-release of catecholamine, are not associated with non-functional paraganglioma. Non-functional tumors have occasionally been found during gynecological exams. Manifestations of vaginal paraganglioma include postmenopausal bleeding, vaginal masses [6, 8, 9], and irregular vaginal bleeding [5, 7, 10], and manifestations of vulval paraganglioma in the form of painful nodules originating from the labia minora [1] and painless nodules under the pubic symphysis [2]. Some paragangliomas, called occult paragangliomas, do not involve hypertension, though the blood tension suddenly increases during the operation [6].

The clinical symptoms of this tumor were non-specific and might have stemmed from an atypical site. This made it difficult to make an accurate preoperative diagnosis. The first critical step is to recognize that any mass originating in

the genital duct may be any paraganglioma [15]. Diagnosis of paraganglioma includes qualitative and localization diagnosis. Biochemical presentation of excessive production of catecholamine is an essential step in the diagnosis of functional paraganglioma. Traditionally, biochemical testing for paraganglioma has relied largely on the measurement of catecholamine levels in urine. These tests have often been carried out in conjunction with measurements of vanillylmandelic acid (VMA) and the metanephrines (normetanephrine and metanephrine) [16]. Accumulating evidence suggests that the measurement of plasma-free metanephrines or urinary-fractionated metanephrines is the most sensitive test for the detection or exclusion of excessive release of catecholamines [17, 18].

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) are traditional positioning measurements. Because CT scanning and MRI have similar levels of sensitivity (90-100%) and specificity (70-80%), MRI is the preferred procedure for pediatric. The specificity of ¹²³I-metaiodobenzylguanidine (MIBG) scanning can be as high as 95-100%, but it is not widely implemented in clinical practice. Cintigraphy of tumor somatostatin receptor (SSTR) and positron emission tomography (PET) are useful in diagnosis of multifocal, metastatic disease and occult paraganglioma [13]. In a report of vaginal paraganglioma published by Tao Caiv, two paragangliomas were found by PET, one was located in vaginal, another was located in pelvic area.

The pathological diagnosis of paraganglioma is also the gold standard for other tumors. Complete pathological examination, including tumor morphology and structure and specific stains, can help distinguish paraganglioma from other tumors, such as rhabdomyosarcoma, hemangioma, and leiomyoma. This tumor is easily misdiagnosed by FNAC and intra-operative frozen section. Positive result of synaptophysin, chromogranin A, simultaneous is considered diagnostic. Dr. Sheila reported a vaginal paraganglioma in an 11-year-old-girl. She was misdiagnosed with rhabdomyosarcoma by frozen section [5]. Our patient was misdiagnosed with clear cell carcinoma by FNAC. Therefore, the pathological diagnosis should be completed by experienced pathologists.

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Paraganglioma does not respond well to chemotherapy or radiation, so complete surgical resection remains the standard of care [17]. Sufficient preoperative preparation, including oral and intravenous fluids to increase blood volume, is very important. Peri-operative mortality is as high as 30% in the absence of sufficient preoperative preparation. This is due to indefinite diagnosis or misdiagnosis. This rate may drop to less than 3% if there is adequate preoperative preparation [11]. Preoperative alpha-blockage therapy may be a suitable means of decreasing the incidence of life-threatening complications related to the release of excessive catecholamine from the tumor. The combination of calcium channel blockers and β -blockers is usually used to lower blood pressure and reduce the heart rate if a single α -blocker does not work effectively. In addition, the blood supply associated with paraganglioma is extremely rich, Akl successfully used interventional embolization of the uterine artery to reduce bleeding [9].

Paragangliomas are usually benign tumors. Histopathology cannot distinguish between benign and malignant tumors. These tumors should be considered malignant on the basis of neoplasm recurrence, metastasis of lymph nodes or nonchromaffin tissues, and invasion or infiltration to the adjacent apparatus. These are the sole diagnostic criteria. Common metastatic sites include the lymph nodes, lung, liver, and bone. Surgical resection of the metastatic lesions is the primary treatment. MIBG can treat malignant paraganglioma, but it can also be used as postoperative a follow-up measure [19]. Periodic checks and close, lifelong follow-up are of considerable importance for these patients because of the likelihood of progression and metastasis.

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Disclosure of conflict of interest

None.

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