



Glomus Tumor of the Female Genital Tract: Three Cases and Literature Review

Jing Q, Jiang W, Liu T, Li L, Zou J* and Feng M*

Department of Pathology, West China Second University Hospital, China

Abstract

Glomus tumors are unusual, benign tumors usually located in the deep dermis of the extremities, while extremely rare cases are in the female genital tract. Here we report 3 cases of glomus tumor of the female genital tract and review the literature. Case 1 was a 32-year-old woman who presented with vaginal tenderness and dyspareunia of one year and a mass with a 1.0 cm diameter was found. Case 2 was a 45-year-old woman who had a 4 cm, movable nodule in the left labia majora. Case 3 was a 56-year-old woman who presented with a mobile, painless nodule with a diameter of 0.8 cm in the right labia majora for one month. All three patients underwent local excision. The tumor cells of all three patients showed epithelioid and no mitotic figures or nuclear atypia. The tumor cells of case one expressed vimentin, caldesmon, calponin, SMA, and CD34; those of case two expressed vimentin and were focally positive for actin and collagen IV; and those of case three expressed SMA and vimentin, with focal positivity for CD99 and calponin. Case one and case three were diagnosed as glomus tumors and case two was diagnosed as glomus tumor with uncertain malignant potential based on the morphology and immunohistochemical results. Through these cases and a literature review, this report will expand our understanding of the glomus tumors in the female genital tract. Especially for intraoperative frozen sections, the possibility of this tumor needs to be considered to prevent over diagnosis or overtreatment.

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*Correspondence:

Juan Zou, Department of Pathology, West China Second University Hospital, No. 20, Section 3, South Renmin Road, Chengdu, Sichuan Province, China, E-mail: huaxipathzj@163.com

Min Feng, Department of Pathology, West China Second University Hospital, No. 20, Section 3, South Renmin Road, Chengdu, Sichuan Province, China, E-mail: huaxipathfm@163.com

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Keywords: Glomus tumor; Vagina; Vulva; Immunohistochemistry; Frozen Section

Introduction

Glomus tumors are distinctive tumors that resemble the normal glomus body and are a specialized form of arteriovenous anastomosis that regulates heat. Wood reported the first case of glomus tumor with a clinical description of “painful subcutaneous tubercles” in 1812 [1], and Masson first described its histological characteristics in 1924 [2]. Glomus tumors often occur in the subungual area of the finger and typically present as small, bluish red painful nodules [3,4] but can also be found in the bone, vagina, ovary, cervix, and vulva, where the glomus body is usually absent [3,5-9].

Glomus tumors consist of glomus cells, blood vessels, and spindle cells. Histologically, glomus tumors are divided into glomus tumor proper, glomangioma, and glomangiomyoma based on the ratio of the three different components [10]. Most glomus tumors are benign tumors, while some cases still show malignant features or have uncertain malignant potential [11]. Tumors with a deep location and larger than 2 cm in size, atypical mitotic figures, moderate to high nuclear grade and ≥ 5 mitotic figures/50 HPF are diagnosed as malignant glomus tumors [11]. Tumors that do not meet the criteria for malignant glomus tumors but have high mitotic activity and superficial location only, large size only (larger than 2 cm), or deep location only can be diagnosed as glomus tumors of uncertain malignant potential [11].

Glomus tumors have a significant female predominance [4] but are rarely located in the female genital tract. To deepen the understanding of this rare tumor in the female genital tract and improve the diagnosis level, we report 3 cases of glomus tumor of the female genital tract and review the literature. In this report, the clinical and pathological features of a case of a vaginal tumor and 2 cases of vulvar glomus tumor are described, and the literature is reviewed.

Case Series

Case 1

The patient was a 32-year-old woman, para 4, gravida 1, Last Menstrual Period (LMP) three weeks previously, who presented to our hospital with the main complaint of longstanding vaginal

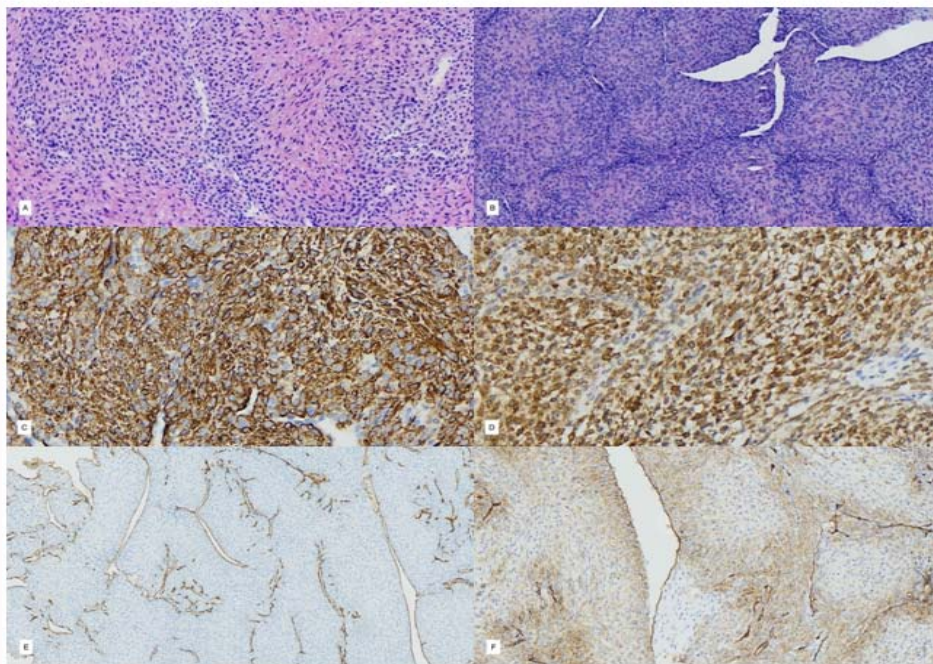


Figure 1: Case 1. Glomus tumor, glomus proper of the vagina. A) Frozen section of glomus tumor showed epithelioid tumor cells diffusely surrounding the thin-walled blood vessels (200X). B) Small, uniform epithelioid tumor cells were around slit-like anastomosing capillaries (H&E 200X). C) Diffuse positivity for caldesmon (400X). D) Diffuse positivity for calponin (400X). E) The endothelial cells of the blood vessels were positive for CD31 (100X). F) The endothelial cells of the blood vessels were positive for CD34 and focally positive for tumor cells (200X).

tenderness and dyspareunia, noted at the time of coitus, of one year duration. The patient denied any abdominal discomfort or vaginal bleeding. The uterus and both adnexal regions were normal, and the cervix was clean. Clinical examination revealed a painful, 1.0 cm diameter mass, thought to be cystic, in the lower one-third of the anterior left wall of the vagina. The mass was tender and very sensitive to touch. Ultrasonography revealed a hypoechoic cystic mass in the lower anterior vaginal wall, measuring approximately 1.0 cm × 1.0 cm × 0.8 cm, and a profuse blood flow signal was detected inside. The mass was mobile, free of surrounding tissue and easily excised completely. Some tissue (1 cm diameter of an unregular firm specimen) was submitted to intraoperative frozen section, which was processed in its entirety. On frozen section, the tumor cells were round, ovoid, or polygonal with a uniform appearance, and the cytoplasm was eosinophilic (Figure 1A). The remaining specimen was unregular, firm tissue with a white-tan cut surface and a size of 1.4 cm × 0.7 cm × 0.5 cm, which was submitted to pathological examination entirely.

On microscopic examination, the nodule was a solid neoplasm composed of uniform, small round cells associated with blood vessels and nerves. At low magnification, patches of tumor cells were distributed around thin-walled blood vessels. At higher magnification, the tumor cells were round to oval and uniform in size. The cytoplasm was eosinophilic. There were no cases of cell atypia or abnormal mitotic figures (Figure 1B). Nerves positive for S-100 could be seen in the center of the tumor, which may be related to the patient's tenderness and dyspareunia.

Immunohistochemistry staining showed that tumor cells expressed vimentin, caldesmon (Figure 1C), calponin (Figure 1D), SMA, CD34, BCL-2, ER and PR. The tumor cells were negative for PCK, EMA, desmin, HMB45, Melan-A, S-100, CD10, CD31 and CD117. The endothelial cells of the blood vessels were positive for

CD31 (Figure 1E) and CD34 (Figure 1F). The Ki67 proliferation index is approximately 5%. Glomus tumor and glomus proper of the vagina were diagnosed.

Case 2

A 45-year-old woman was seen in the gynecologic department for a 4 cm nodule in the left labia majora. The nodule was detected 4 years ago and grew slowly during this period. The nodule was mobile and well defined from the surrounding tissue without pain or other discomfort. The skin over the nodule appeared to be normal and was not sensitive to touch. The nodule was excised in its entirety with clear margins. A 5.0 cm × 3.0 cm × 1.0 cm skin ellipse was received in the pathology laboratory, with the overlying skin being normal. A solid nodule with a diameter of 4.0 cm was seen beneath the skin. The cut section was grayish red with no necrosis or hemorrhage.

At low magnification, a non-encapsulated tumor was located in the dermis, which was poorly demarcated from the surrounding tissue, and the tumor did not involve the epidermis. The tumor cells grew in clusters. Myxoid stroma was present in the intercellular matrix between the tumor cell clusters. Epithelioid tumor cells surrounded capillaries or small blood vessels. The tumor cell clusters around the blood vessels were in small foci. No mitotic figures or nuclear atypia was discerned (Figure 2A).

Immunohistochemistry staining showed that the tumor cells were diffusely positive for vimentin and focally positive for actin and collagen IV, while CD34, caldesmon, CD10, S-100, PCK, EMA, HMB45, calponin, SMA, desmin, and GFAP were all negative. The endothelial cells of the vessels were positive for CD34 (Figure 2B). The Ki67 proliferation index was less than 2%. Glomus tumors with uncertain malignant potential were diagnosed based on the clinical features, morphology and immunohistochemical results.

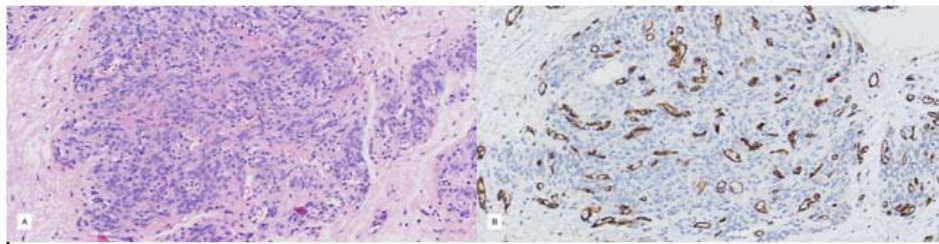


Figure 2: Case 2. Glomus tumor with uncertain malignant potential of the vulva. A) Epithelioid tumor cells surround the capillaries or small blood vessels, without nuclear atypia and abnormal mitotic figures (H&E 200X). B) The endothelial cells of the vessels were positive for *CD34*, while the glomus tumor cells were negative (200X).

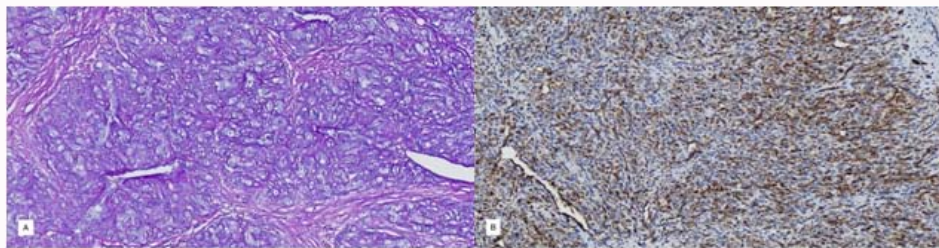


Figure 3: Case 3. Glomus tumor, glomus proper of the vulva. A) Periodic acid–Schiff (PAS) staining accentuated the outlines of epithelioid tumor cells (200X). B) Vimentin diffuse positivity (200X).

Case 3

A 56-year-old postmenopausal woman, gravida 3, para 1, was admitted to the Gynecology Department of our hospital because of a palpable nodule in the vulva for one month. On physical examination, a mobile nodule with a diameter of 0.8 cm was found in the anterior part of the right labia majora. The nodule was painless. There were no abnormalities in the vagina, cervix, uterus, or bilateral adnexa. The nodule was completely excised and submitted for histopathological examination. On macroscopic examination, the specimen was a tan-colored firm, circumscribed mass measuring 1.5 cm × 1.0 cm × 0.4 cm, with a white–gray cut surface and without hemorrhage or necrosis.

At low magnification, the nodule was composed of nested epithelioid tumor cells, with a well-defined margin with a thin fibrous pseudocapsule, and the tumor cell nests were separated by fibrous septa. Large, thickened-wall blood vessels were seen around the tumor nests. At higher magnification, the tumor cells were epithelioid and diffusely distributed around the thin-walled vascular vessels, and the nuclei were round or oval, with a moderate amount of cytoplasm, distinct borders, and inconspicuous nucleoli. Cytological atypia was minimal, and no mitotic figures were found. Periodic Acid–Schiff (PAS) staining accentuated the outlines of the epithelioid tumor cells (Figure 3A).

Immunohistochemistry staining showed epithelioid tumor cells positive for SMA and vimentin (Figure 3B) and focally positive for *CD99* and calponin but negative for *CD34*, caldesmon, *CD10*, S-100, HMB45, EMA, PCK and desmin. The expression of *CD34* and collagen IV confirmed the intimate relationship of the tumor nests to vessels but did not mark epithelioid glomus tumor cells. The Ki67 proliferation index was less than 5%. It was diagnosed as a glomus tumor and glomus proper of the vulva histopathologically and confirmed by immunohistochemistry.

Discussion

Glomus tumors are uncommon benign vascular lesions

considered to be vascular hamartomas derived from the Sucquet-Hoyer canal, an isonym of the glomus body [12]. Glomus tumors account for less than 2% of soft tissue tumors [13,14] and generally occur in the extremities, affecting approximately twice as many women as men [14]. Most of the tumors ranged from 0.2 cm to 5.6 cm in diameter [14–16]. Over 90% of patients present with symptoms of tenderness or pain of varying degrees and are generally sensitive to touch or pressure [4,14]. Typical dermal glomus tumors may be extremely painful [17]. Glomus tumors of the female genital tract can present as painless or painful, and some cases were found accidentally because of other tumors. Glomus tumors can appear as cystic or solid masses depending on the angiomatous component. Due to the rarity of glomus tumors in the female genital tract, it is necessary to carefully distinguish it from other mesenchymal tumors by morphology and immunohistochemical staining to prevent misdiagnosis, especially in intraoperative frozen sections, and to prevent over treatment. Therefore, we report 1 case of vaginal glomus tumor (case one), 1 case of vulva glomus tumor of uncertain malignant potential (case two), and 1 case of vulva glomus tumor (case three).

We report the first case of frozen section of glomus tumor. The frozen sections of case one in our report showed that the nuclei of tumor cells were round or ovoid, with uniform morphology, abundant eosinophilic cytoplasm, unclear boundaries between cells, no mitotic figures and cell atypia, and tumor cells surrounding the thin-walled vascular cavity. When the above morphological characteristics were observed in the frozen sections, this tumor should be taken into consideration so as not to be diagnosed as perivascular epithelioid cell tumor (PEComa), squamous carcinoma or other malignant tumors, which will lead to unnecessary overtreatment of patients. The diagnosis given by our doctor during the operation of case one was mesenchymal tumor, and H&E and immunohistochemistry staining were required to clarify its histological type. The tumor cells on H&E staining were consistent with those of the frozen sections but had epithelioid morphology and slightly larger nuclei, and the cytoplasm was more basophilic.

Table 1: Clinicopathological characteristics of the three cases in our report.

Case	Age (y)	Location	Size (cm)	Symptom	Treatment	Diagnosis	Immunohistochemistry
1	32	Vagina	1.4	Vaginal tenderness and dyspareunia of 1 year	Surgical excision with clear margin	Glomus tumor	Positive: vimentin, caldesmon, calponin, SMA, CD34, Bcl-2, ER and PR. Negative: PCK, EMA, desmin, HMB45, Melan-A, S-100, CD10, CD31 and CD117. Ki67 approximately 5%
2	45	Vulva	4	Mobile but painless nodule in the left labia majora for 4 years	Surgical excision with clear margin	Glomus tumor with uncertain malignant potential	Positive: vimentin, and focally positive for actin and collagen IV. Negative: CD34, caldesmon, CD10, S-100, PCK, EMA, HMB45, calponin, SMA, desmin, GFAP. Ki67<2%
3	56	Vulva	0.8	A palpable nodule in the vulva for 1 month	Surgical excision with clear margin	Glomus tumor	Positive: SMA, vimentin, focally positive for CD99 and calponin. Negative: CD34, caldesmon, CD10, S-100, HMB45, EMA, PCK, desmin. Ki67<5%

AR: Androgen Receptor; EMA: Epithelial Membrane Antigen; ER: Estrogen Receptor; GFAP: Glial Fibrillary Acidic Protein; MSA: Muscle-Specific Actin; PCK: Pancytokeratin; PR: Progesterone Receptor; SMA: Smooth Muscle Actin

Table 2: Clinicopathological characteristics of glomus tumors with uncertain malignant potential reported in the female genital tract.

Case	Author, y	Age (y)	Location	Size (cm)	Clinical manifestations
1	Mark Spitzer [20], 1985	34	Vagina	4	Heavy vaginal bleeding of 4 days duration. Tumor excision was performed.
2	Sonobe [21], 1994	46	Vulva	3	A painful nodule in the periurethral area of the vulva. Tumor excision was performed. No recurrence for >10 years. IHC positive: vimentin, SMA, negative: desmin, cytokeratin, and factor VIII-related antigen.
3	Neriman [6], 2001	54	Ovary	2.5	Routine gynecological exam revealed a right adnexal mass. TAH and BSO were performed. IHC positive: SMA and vimentin; negative: cytokeratin, desmin, MSA, and inhibin; CD34, CD31, and Factor VIII stained vascular endothelium.
4	Stephen P. Slone [22], 2010	73	Ovary	4	Asymptomatic, incidental finding. She underwent laparoscopic RSO, omental biopsy, and right pelvic and para-aortic lymph node biopsies. Medical history: TAH and LSO for benign ovarian cyst, craniotomy for meningioma. IHC positive: SMA, MSA, CD31, CD34, BCL2 (focal), and CD99 (focal); negative: desmin, MART1, S100, thrombomodulin, AE1/AE3, HMB45, synaptophysin, chromogranin, and inhibin. MIB1<2%.
5	Smita Mahapatra [18], 2013	39	Vulva	3	Painful swelling in vulva for six months. Simple surgical excision was performed. IHC: SMA (+++), cytokeratin (-). Follow-up for 12 months, no recurrence.
6	Lee [19], 2018	42	Ovary	8	Postcoital bleeding, found a complex mass in the left adnexal on ultrasound. A laparoscopic LSO was performed. IHC: positive for SMA.
7	Our case 2	45	Vulva	4	Mobile but painless nodule in the left labia majora for 4 years. Surgical excision with clear margin. IHC positive: vimentin and focally positive for actin and collagen IV; negative: CD34, caldesmon, CD10, S-100, PCK, EMA, HMB45, calponin, SMA, desmin, and GFAP. Ki67<2%.

AR: Androgen Receptor; BSO: Bilateral Salpingo-Oophorectomy; EMA: Epithelial Membrane Antigen; ER: Estrogen Receptor; HSIL: High-Grade Squamous Intraepithelial Lesion; IHC: Immunohistochemical Staining; LSO: Left Salpingo-Oophorectomy; MSA: Muscle-Specific Actin; NA: Not Available; PR: Progesterone Receptor; RSO: Right Salpingo-Oophorectomy; SMA: Smooth Muscle Actin; TAH: Total Abdominal Hysterectomy

Case two of our report had a diameter of 4 cm, which was larger than 2 cm, and was diagnosed as glomus tumor with uncertain malignant potential according to the diagnostic criteria [11], and this case was the seventh case. The tumor cells did not show other malignant features, such as abnormal mitosis and cell atypia. Unfortunately, follow-up information was not obtained. Glomus tumors with uncertain malignant potential were previously diagnosed in the female genital tract [18,19]. However, according to the current diagnostic criteria, tumors with diameters larger than 2 cm can only be diagnosed with uncertain malignant potential. There were 7 cases of glomus tumors of uncertain malignant potential in the female genital tract [6,18-22], including our case two.

We reviewed the literature on glomus tumors of the female genital tract, including 11 cases of vulva, 8 cases of vagina, 3 cases of cervix, 1 case of uterus and 5 cases of ovary, and summarized their clinicopathological characteristics in Table 1, 2. The 3 cases of our report were included, and a total of 27 cases have been reported. The age of diagnosis ranged from 29 to 73 years (mean age 46.9 years, median age 45 years). The median size was 1.4 cm, and the average size was 1.9 cm, with a range from 0.1 cm to 8 cm. Among the 27 cases of glomus tumor, 3 cases (11.1%) were diagnosed as glomangiomyoma, 2 cases (7.4%) were diagnosed as glomus tumor with uncertain

malignant potential, the remaining 22 cases (81.5%) were glomus tumor, glomus proper, and none were diagnosed as malignant.

Glomus tumors in these locations can be discovered incidentally [6,22-25] or with varied symptoms, such as vaginal tenderness [8,17], dyspareunia [8,21], vaginal bleeding [5,17,19,20,26], vulvar pain [7,18,21,27-30], or painless masses [9]. Patients who were asymptomatic and had tumors found incidentally usually had tumors located in the cervix [5,25], vagina [9] or ovary [6,22-24]. Cases discovered accidentally were accompanied by cervical squamous carcinoma [23], cervical high-grade squamous intraepithelial lesion [25], endometrioid adenocarcinoma [24], or leiomyomas of the uterus [5]. Although the tumor is usually benign and always small, most cases have diameters smaller than 1 cm, so care needs to be taken to prevent missed diagnosis.

Glomus tumors generally present with typical morphology and immunohistochemical patterns, and their diagnosis is not difficult. To accurately diagnose glomus tumors of the female genital tract, some diseases also need to be differentiated, such as epithelioid gastrointestinal stromal tumors, epithelioid leiomyoma, PEComa, carcinoid tumor, sweat gland adenomas and granular cell tumors. Epithelioid gastrointestinal stromal tumors always show immunoreactivity for CD117 and mutation sequences of exons 9 or

11 of the c-kit gene but usually lack calponin or SMA expression [31]. PEComas generally appear as clear cells and express HMB45, while glomus tumors may co-express alpha-smooth muscle actin and CD34 [10]. The blood vessels in glomus tumors are generally capillaries, while the blood vessels in epithelioid leiomyomas are generally larger with thickened walls. In addition, epithelioid leiomyoma always co-express smooth muscle actin, muscle-specific actin and desmin but lacks CD34 and collagen type IV expression [25,32]. Carcinoid tumors generally express a variety of neuroendocrine markers but usually lack collagen type IV, SMA or MSA expression [5,25]. Granulosa cell tumors are rich in eosinophilic granular cytoplasm and positive for S-100 immunolabeling. The vascular pattern of glomus tumors and the absence of glandular lumens distinguish them from sweat gland adenomas [7].

Although the histomorphology and immunophenotype of glomus tumors have been well described, the etiology and genetic features of glomus tumors are poorly understood. Glomus tumors of the female genital tract are very rare and there are only case reports; there are currently no genetic studies, but studies on gene mutations in glomus tumors occurring in other locations can be referred to. Few studies have shown that the BRAF V600E mutation may be related to glomus tumors (12/126 cases), and most of them are malignant glomus tumors (4/12, 33%) or those with uncertain malignant potential (5/12, 42%) [33-36]. Studies have revealed that familial glomus tumors may be related to the VMGLOM gene, located at 1p21-p22, and the TIE-2 gene [37-39]. Another study detected the MIR43-NOTCH fusion gene in glomus tumors, where the MIR43 gene is located at 5q32, NOTCH2 is located at 1p13, and NOTCH1 is located at 9q34 [40]. Some glomus tumors may also be associated with neurofibromatosis type 1 [41,42].

Simple lumpectomy is an appropriate treatment for glomus tumors, even for those with uncertain malignant potential [14,18]. For those with lesions in the vulva or vagina and complaints about pain or other symptoms, resection with a clear margin can completely relieve the symptoms [7,17,18]. Cases discovered accidentally after total hysterectomy [6], salpingo-oophorectomy [22-24] or cervical cold-knife conization [25] generally do not require additional treatment after the surgery if the mass is removed completely. However, for those with malignant features or with uncertain malignant potential features, re-excision is necessary to ensure clear margin, and patients should be followed-up closely to ensure timely treatment in cases of recurrence or metastasis [11]. The outcomes of glomus tumors are usually good [4]. Recurrence was rare and only happened if the mass was incompletely excised [14,20].

Conclusion

Glomus tumors of the female genital tract are rare benign lesions, but they should also be considered as a possible diagnosis of mesenchymal neoplasms, especially for intraoperative frozen sections. The possibility of this tumor needs to be considered to prevent over diagnosis or overtreatment. Lumpectomy with negative margins is generally curative. The morphology and immunophenotype of glomus tumors of the female genital tract have been well described, but the etiology and gene mutations have not been studied. More studies on the gene mutations and histogenesis of this disease are needed, especially for those with malignant and uncertain malignant potential.

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