



Analysis of clinical outcomes of patients with primary rare carcinoma of Bartholin gland: six case series report and review of the literature

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Background: Bartholin gland carcinoma (BGC) is an unusual malignancy representing less than 5% of all vulvar carcinomas. Due to the limited published information on the diagnosis and treatment of BGC, this tumor is prone to misdiagnosis; most cases are found in an advanced stage once the diagnosis is delayed.

Methods: This was a retrospective study of six patients with BGC in the West China Second University Hospital between January 2011 to August 2021.

Results: In our study, BGC was 4.4% in all vulvar malignancies. The average age of six patients was 40.83 years old, with the tumor size ranging from 2 to 5 cm, and time of onset ranging from 2 to 3 years. Based on the retrospective clinical staging, there were three patients in stage I, one in stage II, and two in stage IVb. The human papillomavirus (HPV) 16 was detected in tissue samples of three patients. Two patients with excision of the vulvar mass and wide local excision (WLE) had local recurrence at 32 and 18 months, respectively. One patient died of distant metastasis of tumor, one died of non-tumor cause, and the others survived to this day.

Conclusions: Six patients with BGC were reviewed in this study, and their characteristics of baseline information, clinicopathology, treatment approaches, and prognosis were described and analyzed, hoping to provide new insights for the diagnosis or treatment in this rare malignancy.

Keywords: Bartholin gland carcinoma (BGC); squamous cell carcinoma (SCC); human papillomavirus (HPV); diagnosis; treatment

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Introduction

Bartholin gland carcinoma (BGC) is an extremely unusual malignancy that is rarely reported in the previous literature. Given this, this tumor is easily misdiagnosed and just be regarded as an inflammatory mass or ordinary vestibular gland cyst that causes a poor prognosis due to a delayed diagnosis and treatment. BGC may arise either from the duct and the vestibular orifice of a Bartholin gland or from

the gland itself, giving rise to multiple histologic subtypes: squamous cell carcinoma (SCC) (30.7%), adenoid cystic carcinoma (29.6%), adenocarcinoma (25%) or less common subtypes (1). It is widely known that human papillomavirus (HPV) infection is a high-risk factor for cervical, vaginal, and vulvar tumors (2). As one of the rare forms of vulvar malignancy, the association of BGC with high-risk HPV infection is still unclear. Previous studies have confirmed

Table 1 Clinical characteristics of six patients with Bartholin gland carcinoma

No.	Age, years	Gravidity and Parity	Perineal surgery history	The onset time	Histology	Grade	Side and size	Clinical stage	Surgery	Chemotherapy and radiotherapy
1	36	G1P1	Ostomy of Bartholin's gland cyst	2 years	Papillary squamous cell carcinoma	3	Left, 5 cm	IVb	RV + BILND + LPLND + PLB	Chemo with BP, RT
2	28	G1P1	Episiotomy	2 months	SCC	2~3	Left, 3 cm	I	Excision of vulvar mass	–
3	57	G2P1	No	6 months	Adenosquamous carcinoma	–	Right, 2 cm	II	WLE + BILND	Chemo with PC, RT
4	46	G4P3	Episiotomy	1 year	SCC	3	Left, 2 cm	I	WLE + BILND	RT
5	34	G3P1	Episiotomy	3 years	SCC	3	Left, 4×3 cm	IVb	RV + BILND + LPLND	Chemo with PC, RT
6	44	G7P1	No	1.5 years	SCC	3	Left, 3 cm	I	Excision of vulvar mass	–

SCC, squamous cell carcinoma; RV, radical vulvectomy; WLE, wide local excision; BILND, bilateral inguinal lymph node dissection; LPLND, left pelvic lymph node dissection; PLND, pelvic lymph node dissection; PLB, para-aortic lymph node biopsy; Chemo with BP, chemotherapy with DDP (Cisplatin) and Paclitaxel; Chemo with PC, chemotherapy with Paclitaxel and Carboplatin; RT, radiotherapy.

that HPV infection plays a role in the pathogenesis of vaginal and vulvar dysplasia, and human papillomavirus 16 (HPV16) accounts for most HPV-positive cases (3,4). However, there are limited published data on the diagnosis and treatment of BGC and its association with HPV. Here, in our study, we selected 6 cases of primary BGC and analyzed the clinical outcomes of these patients combined with previous literature reviews. We present the following article in accordance with the AME Case Series reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2591/rc>).

Methods

This was a retrospective study. The medical records of six patients with BGC who were admitted to the West China Second University Hospital between January 2011 and August 2021 were reviewed. The diagnosis of these patients was based on gynecological examination and pathological biopsy, and retrospective clinical staging was used according to the staging classification from the International Federation of Gynecology and Obstetrics (FIGO) staging. The study was conducted following the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the West China Second University Hospital (No. 017) and informed consent was taken from all the patients.

Results

Records were reviewed from the aspects of the clinical and tumor characteristics, treatment, along with outcomes and recurrences of six patients (*Table 1*). Six patients with BGC aged from 28 to 57 years old (average age: 40.83 years old). Two of the six patients had undergone lateral episiotomy incision, and the other four received cesarean section. The main clinical manifestations of BGC were vulvar lumps, dyspareunia, and pain. All the patients presented with a mass or lump in the Bartholin's gland area. The time from the appearance of mass to seek medical advice was from 2 months to 3 years (average: 16.3 months).

Of the six patients, one lesion was located on the right and the other five were on the left. Three patients had a history of spontaneous labor and had undergone lateral perineal episiotomy, and only one patient had an ostomy history of Bartholin's gland cyst. Because three patients had a history of lateral perineal episiotomy and all the perineal masses were located on the left. When a mass was found, endometriosis of the perineal incision site had been considered primarily. Therefore, one of them did not decide on surgical treatment until one year after the mass was found, the postoperative pathology showed SCC of the Bartholin gland. Of these six patients, the tumor size ranged from 2 to 5 cm. According to the pathologic review, there were four cases of SCC (three poorly differentiated and one moderately-poorly differentiated), one case of

Table 2 The postoperative pathology and outcomes of six patients with Bartholin gland carcinoma

No.	Resection margin	Lymph node metastasis	Perineural invasion	Intravascular cancer embolus	HPV	Follow-up	Local recurrence	Distant metastasis
1	Positive	Positive	Positive	Positive	16 (+)	NED, 25 months	Negative	Negative
2	Negative	NA	Negative	Negative	–	Local recurrence, 32 months; DOD, 74 months	Positive	Positive (lung)
3	Negative	Negative	Positive	Positive	–	DONR, 28 months	Negative	Negative
4	Negative	Negative	Negative	Negative	–	Local recurrence, 18 months*	Positive	Negative
5	Negative	Positive	Positive	Positive	16 (+), 58 (+)	NED, 5 months	Negative	Negative
6	Negative	NA	Negative	Negative	16 (+)	NED, 3 months [†]	Negative	Negative

*, one and a half years after operation, this patient was found a solid mass (1.5 cm) occupying the left vaginal wall near the vaginal orifice. The second operation was performed with partial resection of vulvar mass and laparoscopic pelvic lymph node biopsy. Postoperative pathological examination showed local recurrence of the tumor but no pelvic lymph node metastasis; [†], this patient was suggested to undergo second operation and chemoradiotherapy, she did not receive further treatment up to now due to some family reasons. NA, not applicable; HPV, human papillomavirus; NED, no evidence of disease; DOD, died of disease; DONR, died of nonrelated disease.

papillary SCC, and one case of adenosquamous carcinoma. In these six cases, one case of carcinoma extended to the deep musculature and vagina, and two cases of carcinoma metastasized to ipsilateral pelvic lymph nodes. Based on the retrospective clinical staging, there were three patients in stage I, one in stage II, and two in stage IVb (*Table 1*).

For two patients with stage IVb and the size of perineal mass both more than 3 cm, the preoperative imaging examination revealed enlarged pelvic lymph nodes, and both of them performed an extensive surgical procedure [radical vulvectomy, bilateral inguinal lymph node dissection (BILND), and left pelvic lymph node dissection (LPLND)]. For the one with a perineal mass up to 5 cm, a para-aortic lymph node biopsy was simultaneously performed, and the para-aortic lymph node was negative but the pelvic lymph nodes were positive. Two patients with 2 cm perineal mass underwent wide local excision (WLE) and BILND, and the pelvic lymph nodes were negative. In the other 2 patients, only excision of the vulvar mass was performed, and a second operation and chemoradiotherapy were suggested but the patients refused. A 28-year-old woman with negative tumor resection margins recurred 32 months later. After the first operation (excision of vulvar mass), the patient refused a second expanded surgery and/or chemoradiotherapy for fear of loss of sexual function. Another patient with excision of vulvar mass also did not receive further treatment up to now due to some family reasons. As noted, the HPV16 was detected in tissue samples of three patients (*Table 1* and *Table 2*).

The outcomes of six patients with BGC were shown in *Table 2*. Two patients with excision of vulvar mass and WLE had a local recurrence at 32 and 18 months, respectively. The first one died at 64 months with lung metastasis, 3.5 years after completion of treatment. Case 2 was found a solid mass (1.5 cm) occupying the left vaginal wall near the vaginal orifice 1.5 years after the operation and the second operation was performed with partial resection of the vulvar mass and laparoscopic pelvic lymph node biopsy. Postoperative pathological examination showed local recurrence of the tumor but no pelvic lymph node metastasis. One patient died 28 months after completion of treatment with no evidence of disease due to stroke. Excluding these three patients, the other three patients were alive with no evidence of disease.

Discussion

Nowadays, the most common histologic subtype of carcinoma arising in the Bartholin's gland is SCC, which accounts for approximately 40% of these neoplasms (5). BGC primarily affects postmenopausal women, and the median age at diagnosis is reported to be 50–57 years (6). In the early stage of onset, the main manifestation of BGC is a painless mass at the back of the labia majora. Because of its nonspecific symptoms, BGC is often misdiagnosed as a cyst or an abscess, and the diagnosis is delayed until is covered at later stages. In our study, the time from

the appearance of mass to seek medical advice was from 2 months to 3 years (average: 16.3 months). Three patients had a history of lateral perineal episiotomy, and their perineal masses were all located on the left. When a mass was found, the endometriosis of the perineal incision site had been considered primarily. Additionally, one patient had an ostomy history of Bartholin's gland cyst. Based on this, these patients cannot get the best treatment in time.

BGC is a malignant tumor located in the vulva, and the infection of high-risk HPV could be the cause of this disease. There have been some reports about the etiologic role of high-risk HPV, especially the role of HPV16, in the pathogenesis of SCC of the Bartholin gland recently (4,7,8). In our cases, all patients with SCC components were found, including three SCCs (three poorly differentiated and one moderately-poorly differentiated), one papillary SCC, and one adenosquamous carcinoma. The HPV16 was detected in tissue samples of three patients. To date, the number of cervical and vulvar SCC may be prevented by the current HPV vaccines.

Because the existing retrospective studies are limited, there is no definite recommendation for the best treatment of BGC. Although surgery remains the cornerstone of treatment in median vulvar tumors, until now, there has been no evidence of the benefits of performing more aggressive surgical procedures or of an advantage of surgery over radiation in the treatment of BGC, and no consensus has been reached on the need for lymph node dissection (5,6). Furthermore, it is worth noting that current research has shown that BGC affects predominantly postmenopausal women and that radical surgery is more receptive to older populations than younger patients (9). Our patients with BGC aged ranging from 28 to 57 years old, and the tumor size ranged from 2 to 5 cm. Two young patients were both very resistant to radical vulvectomy and radiotherapy (RT) by fearing loss of sexual function or due to some other family reasons. Although the resection margin of the tumor was negative in a 28-year-old patient, the recurrence occurred 32 months later. As for the others, two patients were treated with WLE and BILND, one of them with stage II followed by chemotherapy and RT; two patients were treated with radical vulvectomy, BILND, and pelvic lymph node dissection, and then both followed by chemotherapy and RT.

It has been reported that less radical surgery plus RT achieves good long-term survival and has fewer complications, and WLE followed by RT is considered as the best treatment for advanced primary BGC (10).

However, for some non-SCC, the effect of RT and chemotherapy is not exact. It is also reported that a 92-year-old woman received RT alone for the metastasis of mucinous adenocarcinoma of the Bartholin gland to the right inguinal lymph node. Despite intensive radiation therapy, the tumor recurred locally and the patient died 10 months after RT (11). In our study, one patient with SCC at stage I was treated with WLE and BILND followed by RT without chemotherapy, the tumor was local recurrence in 18 months after RT.

Bone and lung are the most common sites of distant recurrence (11,12). Lymph node metastasis directly affects the postoperative stage of patients. Inguinal femoral lymph node status strongly affects patients' survival (13). Of our 6 patients, four patients underwent lymphadenectomy. The pelvic lymph node metastasis was found in two of them, and the postoperative stage was IVb. Therefore, they received routine RT and chemotherapy after the operation. They had no local recurrence or distant metastasis until now.

In conclusion, BGC is a very rare malignant tumor and usually presents in an advanced stage that the local and distant metastases are frequent when the diagnosis and treatment are delayed. Here, we reported six patients with BGC, and their characteristics of baseline information, clinicopathology, treatment approaches, and prognosis were described and analyzed, hoping to provide new insights for diagnosis or treatment in this rare malignancy.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2591/rc>

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have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted following the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the West China Second University Hospital (No. 017) and informed consent was taken from all the patients.

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