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Case Report
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Adenoid Cystic Carcinoma of Bartholin's Gland: A Case Report and Literature Review

Xuetao Hou[1], Lingling Xie[2], Yan Ding[1], Min Li[1], Yongpai Peng[2] and Huaiwu Lu[2]**

[1]Department of Gynecology, Jinan Second Maternal and Child Health Care Hospital, China

[2]Department of Gynecologic Oncology, Sun Yat-sen University, China

Abstract

Adenoid Cystic Carcinoma (ACC) of Bartholin's gland is a very rare malignant tumor of the vulva, which characterized by slow growth, local infiltration, late recurrence and distant metastasis. Surgical treatment is the first choice for the treatment of ACC of Bartholin's gland, but there is no consensus on the best surgical treatment. Extensive local resection and radical resection with or without lymph node resection can be performed according to the patient's condition. The authors reported the case of a 52-year-old woman with ACC of Bartholin's gland received surgical treatment and chemotherapy. She underwent radical local vulvectomy plus left superficial inguinal lymphadenectomy. Actin and S-100 in partial cells and CK, CEA, P63 and EMA were positive immunohistochemically. Due to the suspicion of recurrence, the patient underwent simple lesion resection again after the completion of the third course of paclitaxel (135 mg/m^2) and carboplatin (AUC 6) chemotherapy. There was no evidence of recurrence for the patient after 41 months of follow-up.

Keywords: Adenoid cystic carcinoma; Bartholin's gland; vulvectomy; Chemotherapy

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Correspondence:
Yongpai Peng, Department of Gynecological Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, NO.107, Yan-jiang West Road, Guangzhou, 510120, China; E-mail: pengyongpai@qq.com
Huaiwu Lu, Department of Gynecological Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, NO.107, Yan-jiang West Road, Guangzhou, China, 510120; E-mail: luhuaiwu@163.com

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Introduction

Vulvar malignancies account for 3% to 5% of all primary gynecological malignancies and are most common in elderly women [1]. Squamous cell carcinoma is the most common, but adenoid cystic carcinoma is rare. Adenoid Cystic Carcinoma (ACC) of Bartholin's gland accounting for about 10% of all primary malignant tumors of Bartholin's gland [2]. Since the first description of a Bartholin's gland carcinoma, there are about 100 cases reported in the literature at present, so there is no large randomized controlled case study and no unified treatment regimen. One case of Adenoid Cystic Carcinoma of Bartholin's Gland (BG-ACC) was treated in our hospital. This case was presented with a review of the relevant literature.

Case Presentation

The patient, a 52-year-old gravida 3 para 1 yellow female, post-menopausal for 2 years, presented with palpable nodular mass in left labia majora that had appeared 6 years earlier and was pathologically suggested to be cancerous for 20 days. She was admitted to the Department of Gynecologic oncology, Sun Yat-sen Memorial Hospital in June 2008. The nodular mass was first discovered when it was about the size of peanuts in 2002, increasing in recent years. Pathological biopsy of the lesions was performed in peripheral hospital about 20 days ago. The pathologic results were considered Adenoid Cystic Carcinoma (ACC) for that the boundary of the lesion was unclear, and the epithelial cells were arranged in small strands. Small glandular ducts and cribriform structures showed infiltration growth, and perineural invasion was suspected. Pelvic and vulvar MRI showed an irregular mass on the left side of vagina, about 33 mm × 29 mm × 18 mm. The mass obviously compressed the external orifice of urethra, and no lymph node enlargement was found. There was no abnormal vaginal bleeding or fluid drainage after menopause. Physical examination: an irregular mass, about 4 cm × 3 cm, was touched in the left labia majora, which has clear boundary, poor mobility, mild tenderness and no midline crossing. Contralateral side and vaginal and uterine appendages were normal. The patient's tumor markers including SCCA, AFP, CEA, CA125, and CA153 and CA724 were within normal limits. On June 16, 2008, the patient underwent radical local vulvectomy plus left superficial inguinal lymphadenectomy under epidural anesthesia. Post-operative specimen revealed that the tumor was tough, with uniform pale section, visible vortex spline structure, clear boundaries between tumor and the surrounding tissues, no

Table 1: The clinical details and follow-up of patients with adenoid cystic carcinoma of Bartholin's gland reviewed in the literature.

References	Patients	Age At diagnosis	Tumor location	Radiological examination before surgery		Pathology		Primary treatment	Pathology		Local Recurrence	Distant Metastasis	End	
				Lymph node metastasis	Distant Metast-asis	Surgical margin	Neural invasion		Surgical margin	Lymph node metastasis			Follow-up time(m)	Status at last follow-up
S.Vandeginste	1	36	Right	+	-	+	+	RV + BILND	-	+	N	Bone + Thorax	29	Died with metastatic disease
	2	70	Right	-	-	+	+	Hemivulvectomy + IILND	-	-	N	N	11	NED
V. Anaf	3	52	Left	Un	Un	Un	Un	LE+ IILND	Suspicious positive	-	Y	N	15	SD
Mustafa Aziz	4	59	Right	-	-	Un	Un	LE+ RT + PV	Un	-	N	Brain	25	SD
Kaei Nasu	5	54	Left	-	-	+	+	RV + inguinal and pelvic lymphadenectomy	-	-	N	N	60	NED
Fang-Yu Hung	6	49	Left	Un	Un	Un	Un	RV + BILND	-	-	N	N	18	NED
Sook-Young	7	43	Left	-	-	+	+	Radical hemivulvectomy including residual tumoral tissue with approximately 2 cm resection margins + IILND +RT	-	-	N	N	17	NED
	8	50	Right	Un	Un	Un	Un	LE	-	-	N	Lung	10	SD
Ozgu r s, ahincioglu	9	64	Left	-	-	+	Un	hemivulvectomy including residual tumoral tissue with approximately 2 cm resection margins + IILND	-	-	N	N	6	NED
I Alsan Cetinn	10	40	Left	Un	Un	Un	+	LE	Un	Un	Y	Lung + Thorax	166	SD
Eriko Takatori	11	68	Left	Un	Un	+	Un	LE + chemoradiotherapy (RT+ CPT-11)	+	-	N	N	24	NED
Tseh-Lee C	12	53	Left	-	-	+	Un	Radical hemivulvectomy including residual tumoral tissue with approximately 2 cm resection margins+ BILND	-	-	N	N	36	NED
L.Agolli	13	54	Right	Un	Un	+	+	radical hemivulvectomy + IILND + RT	-	-	N	N	20	NED
Rajeev Ramanah	14	48	Left	Un	Un	+	Un	radical tumor re-excision + IILND + RT	-	+	N	Brain +Lung	31	Death with metastatic disease
Marek Nowak	15	44	Left	Un	Un	+	+	RLE + BILND + PV+ RT	-	-	Y	Lung	173	Death with metastatic disease
Mojgan Akbarzadeh-Jahromi	16	42	Left	-	Un	+	+	LE + RT	+	-	N	N	19	NED
Leena Rose Johnson	17	42	Un	-	Un	Un	Un	RV + ILND+RT	+	-	Y	Lung	129	SD
	18	32	Un	-	Un	Un	Un	RV + RT	+	-	Y	Lung	51	Death with metastatic disease
	19	43	Un	-	Un	Un	Un	RV	-	-	N	N	11	NED
	20	38	Un	-	Un	Un	Un	RV + RT	+	-	N	N	8	NED

Abbreviations: Un: Unavailable; +: Positive; -: Negative; LE: Local Excision; RLE: Radical Local Excision; RV: Radical Vulvectomy; PV: Patial Vulvectomy; IILND: Ipsilateral Inguinal Lymph Node Dissection; BILND: Bilateral Inguinal Lymph Node Dissection; RT: Radiotherapy; SD: Stable Disease; NED: No Evidence of Disease

obvious hemorrhage, necrosis and capsule. Pathologically, the tumor was adenoid cystic carcinoma of Bartholin's gland accompanied with blood vessels, nerves and smooth muscle tissue invasion and no metastasis of inguinal lymph nodes. Immunohistochemically, Actin and S-100 in partial cells and CK, CEA, P63 and EMA were positive. According to FIGO (the International Federation of Gynecologists and Obstetricians) 1988 staging standard, the pathological staging was stage II. The patient received paclitaxel (135 mg/m^2) and carboplatin (AUC 6) intravenous chemotherapy every three weeks after surgery. After 2 courses of chemotherapy, a painful nodular masses was found on the perineum near the anus with diameter 2.5 cm. MRI revealed that the mass on the left labia majora was about 2 cm × 2.2 cm and the boundary was unclear which suggested local recurrence. Simple lesion resection was performed after the third course of chemotherapy without pathological evidence of recurrence. The patient was then followed up to 41 months postoperatively and there was no evidence of recurrence.

Discussion

Adenoid Cystic Carcinoma (ACC) is a special type of adenocarcinoma, which is common in salivary gland, respiratory tract and digestive tract. ACC primarily occurring in Bartholin's gland is really rare. ACC represents 10% of Bartholin's gland carcinomas, which in themselves account for 2% to 7% of all vulvar carcinomas and less than 1% of all female genital malignancies [3,4].

The Bartholin's gland is located deep in the labia minor, so the Adenoid Cystic Carcinoma (ACC) of Bartholin's Gland (ACC-BG) has the characteristic of infiltrating into the vagina and deep muscle. The chief complaints and first signs of this neoplasm are usually non-

Table 2: The progression-free time, recurrence site and treatment of patients with adenoid cystic carcinoma of Bartholin's gland reviewed in the literature.

References	Patient	Progression of disease	Progression free time(m)	Relapse site	Treatment
S Vandeginste	1	Distant metastasis	24	Bone + Thorax	RT
		Local recurrenc	48	Vulva	LE
V Anaf	3	Local recurrence	52	Left paracolpium+ rectum + right labia	posterior pelvectomy + left terminal colostomy + radical vulvectomy + pelvic lymphadenectomy + total hysterectomy + ablation of the left ischiorectal fossa
Mustafa Aziz	4	Distant metastasis	16	Brain	A median suboccipital craniectomy+ WBRT (30 Gy in 10 fractions)
Sook-Young	8	Local recurrence	12	Vulva	No further treatment
		Local recurrence	23	Vulva+ vagina	RLE + temporary colostomy
		Local recurrence	47	vulva + right clitoris, urethra and ano-rectal junction	Total pelvic exenteration + RV + left salpingo-oophorectomy + inguinal and pelvic lymphadenectomy + ileal conduit and lower anterior resection with Hartman's colostomy
		Distant metastasis	59	Lung	Metastasectomy
		Recurrent metastasis	63	Lung	Chemotherapy (cyclophosphamide + adriamycin + cisplatin)
I.Alsan Cetinn	10	Local recurrence	36	Vulva	RV +I ILND
		Local metastasis	54	Anal canal + vagina + pelvic bone + ischiopubic bone	Hemivulvectomy + RT
		Distant metastasis	90	Lung	Chemotherapy (cisplatin + ifosfamide + bleomycin)
		Distant metastasis	the last cycles of chemotherapy	Thorax	liposomal doxorubicin + oral cyelophosphamide
Rajeev Ramanah	14	Distant metastasis	24	Brain	WBRT
		Distant metastasis	26	Lung	Metastasectomy +chemotherapy (cyclophosphamide + cisplatin + adriamycin)
Marek Nowak	15	Local recurrence	84	Vulva	Abdominoperineal amputation of the rectum + distal part of the vagina with sigmoideostomy
		Local metastasis	96	contralateral vulva	Lesion resection
		Local metastasis	132	contralateral vulva	Lesion resection
		Distant metastasis	168	Lung	Metastasectomy

Abbreviations: WBRT: Wide Brain Radiotherapy

specific mainly including inflammation, pain, burning sensation, bleeding, dyspareunia and/or palpable mass of labia majora [5,6]. Some patients may have been misdiagnosed as Bartholin's glandular cyst or abscess and have received multiple incisions and drainage and may delay in treatment [7]. It has been reported that the median age of diagnosis of adenoid cystic carcinoma of Bartholin's gland is 49 years old (25-80 years old). Therefore, it is necessary to perform biopsy or resection for early diagnosis in patients aged 40 or older with a nodule involving Bartholin's glands.

Pathology is the golden standard for the diagnosis of the disease. Under the microscopy, there are 3 main growth patterns of cancer cells: cribriform, tubular and solid structure. The most common is the cribriform structure which presents that tumor cells are single small cells arranged in strands with slightly eosinophilic cytoplasm surrounded by extracellular matrix without cellular components. Milchgrub et al. [8] analyzed the pathology and prognosis of 17 patients with ACC of Bartholin's gland, which showed that the histological type of the tumor did not affect the prognosis of the disease. The tumor is derived from epithelium and myoepithelium on immunohistochemical staining. It has been reported that some cases have positive expression of progesterone and estrogen receptor, which is helpful to the future research of hormone therapy [9].

Because of rare cases, there is still no consistent optimal treatment, but most researchers recommend individualized treatment for patients. Hence, we search on the PubMed, review all the ACC-BG literature, and summarize the clinical details of the patients' involved, shown in (Table 1). According to Table 1, surgery is the first choice. Tumor grade, stage, invasion of major nerves, margin status and lymph node metastasis are important prognostic factors of disease progression. Extensive local excision or radical vulvectomy combined with or without inguinal lymphadenectomy is recommended according to the condition, and radical vulvectomy is more recommended for patients with higher risk of relapse [10]. Anaf et al. [11] had proposed that pelvectomy might be candidate methods to palliate pain for patients with advanced pelvi-perineal neoplasms and incapacitating pain or intolerable bleeding and discharge, in whom all other primary treatments were unsuccessful. In addition, resection of the inferior pubic ramus is performed to treat patient with advanced BG-ACC that have invaded the obturator muscle and inferior pubic ramus. This regimen does not require postoperative radiotherapy, but the long-term prognosis needs to be further explored [12].

To date there is no case report of contralateral inguinal lymph node metastasis, and ipsilateral inguinal lymph node metastasis might be present in 10% to 15% of cases. Only 4 cases out of 32 patients with ipsilateral or bilateral lymphadenectomy had lymph nodes metastases which were suspected preoperatively [13-16]. Rajeev Ramanah et al. [17] reported one case with a highly suspicious left inguinal lymph node by MRI scan and high metabolic activity upon PET scan. Some scientists proposed that lymph nodes could be resected only when clinically touched or founded by imaging examination. Therefore, ipsilateral inguinal lymph node dissection is recommended to reduce postoperative complications.

According to a review by Alsan et al. [6], 54% and 46% patients were performed simple excision and radical vulvectomy, respectively. In 57 cases with known resection margins status, the recurrence rate of cases with negative resection margins was 10%, but those with positive resection margins was 35%. Patients with positive margins are more likely to lead to recurrence. Therefore, wide excision is necessary to secure a pathologically enough negative resection margin.

Based on the summary of case reports from all over the world, as shown in (Table 2), radiotherapy seems to have become a routine adjuvant therapy for surgical margin positivity and local infiltration. The research analyzed by Alsan C et al. [6] confirmed it, among patients with negative margins, the recurrence rate was 0% with RT *vs.* 20% without RT, and among patients with positive margins, and the recurrence rate was 14% with RT *vs.* 40% without RT. The sites of metastasis for BG-ACC reported were lung, bone, liver, kidney and brain among which lung was the most common site. Chemotherapy were valuable for metastatic adenoid cystic carcinoma of the salivary and parotid gland [18,19]. Thus chemotherapy was tried to treat metastatic BG-ACC. Chemoradiotherapy with irinotecan (CPT-11) was effective for BG-ACC with manageable adverse events was reported by Eriko Takatori et al. [20]. The reported chemotherapy regimens were Methotrexate, Dactinomycin, Doxorubicin (DXR), Cyclophosphamide (CPA), and CPA+DXR+cisplatin, CPA+DXR. Among the regimens above, cyclophosphamide, Adriamycin and cisplatin regimen were used most frequently.

ACC of Bartholin's gland progressed slowly and presented for long-term local recurrence and distant metastasis. According to the literature, the 5-year and 10-year survival rates of the disease were 71% to 100% and 59% to 100%, respectively [21]. Another literature conducted by Copeland LJ et al. [22] revealed that the progression-free survival rate was 47% at 5 years and 38% at 10 years, respectively. We desire that this report will promote the establishment of effective and systemic therapy for ACC of Bartholin's gland.

Authors' Contributions

Huaiwu Lu and Yongpai Peng were responsible for the design of the study and interpretation of the data. They also have revised critically the manuscript for important intellectual content. Xuetao Hou and Lingling Xie were responsible for the data acquisition and selection. Yan Ding and Min Li were responsible for the data analysis and clinical interpretation of the data. All authors contributed to the writing of the manuscript. All authors read and approved the final version of manuscript.

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