

Case Report

Report of two cases of adenoid cystic carcinoma of Bartholin's gland and review of literature

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Abstract

Objective: Primary adenoid cystic carcinoma (ACC) of Bartholin's gland is a rare gynecologic malignancy. We report two cases from primary treatment to recurrence and the adjuvant treatment.

Case Report: A woman aged 37 years presented with a mass on the right posterior labia minor and underwent right radical hemi-vulvectomy and right-side inguino-femoral node dissection. Final pathology showed ACC arising from Bartholin's gland with positive margins. She received adjuvant external beam radiation to the pelvis, right vulva, and groin area. However, distal metastasis occurred 42 months after initial treatment and she eventually died of multiple metastases. Another woman aged 48 years presented with a mass on the right posterior labia with intermittent pain. She underwent right hemi-vulvectomy and right inguino-femoral lymph node dissection only because pathology showed ACC of Bartholin's gland with negative surgical margins. Lung metastasis occurred 59 months after initial treatment. She took tamoxifen only and achieved stable disease status for 4 years.

Conclusion: To date, about 70 cases have been reported. We treated our second patient with antiestrogen therapy for 4 years and achieved good quality of life and stable disease status. However, further study on hormone therapy for ACC of Bartholin's gland is needed.

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Keywords: adenoid cystic carcinoma; Bartholin's gland; chemotherapy; radiation; radical vulvectomy; recurrence

Introduction

Primary carcinoma of Bartholin's gland is a rare gynecologic malignancy, comprising 0.001% of all female genital malignancies and 2–7% of all vulvar carcinomas [1]. Among all the reported cases, 10–15% had adenoid cystic carcinoma (ACC), which is histologically similar to the adenocarcinoma

of the salivary glands [2]. To date, about 70 cases of ACC of Bartholin's gland have been reported. Herein, we report two cases.

Case reports

Case 1

A 37-year-old female, gravida 5, para 2, presented with a swelling on the right posterior labia minor associated with intermittent tenderness. The patient recalled that the mass had

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slowly increased in size from 2 cm over a period of 12 months just after her second delivery. Physical examination found an indurative, fixed, irregular margin mass of about 4 cm × 3 cm over the right posterior labia minor, just at the site of Bartholin's gland. The mucosa was intact and no pus discharge or bleeding was found. Pelvic bimanual examination revealed a normal cervix, normal uterine size, and no palpable masses in the adnexa. The patient's laboratory data on admission, including complete blood counts and kidney and liver functions, were within normal limits. The chest X-ray was normal. Serum levels of tumor markers CA125 and CEA were also in the normal range before treatment. A simple excision was arranged first, and an intraoperative frozen section of the tumor revealed carcinoma. The patient underwent a right radical hemi-vulvectomy and right-side inguino-femoral node dissection with excision of a portion of the vagina, ischio-rectal fat, a portion of the levator ani and anal sphincter because the firm, irregularly shaped mass extended to the periostem of the inferior pubic ramus with close approximation to the anal sphincter.

The final pathology showed ACC arising from Bartholin's gland. The tumor had invaded deep into the stroma of the vagina with extensive perineural invasion and skeletal muscle infiltration. Immunohistochemical (IHC) stains for the estrogen receptor and progesterone receptor were negative. The margins of the resection were positive. Two of 12 right inguinal lymph nodes were metastatic. An abdomino-pelvic computerized tomography scan 2 weeks after surgery showed no residual mass or abnormal inguinal lymph node enlargement. The patient received postoperative adjuvant external beam radiation (a total of 7000 cGy over 35 fractions) to the pelvis, right vulva, and groin area.

After radiation, she maintained regular outpatient surveillance every 3 months. Unfortunately, distant metastasis was found 42 months after initiation of the adjuvant radiation therapy. The patient complained of right thigh and ankle pain. A technetium-99m-methylene diphosphonate (Tc99m-MDP) whole body bone scan revealed multiple bone metastases. An irregular mass lesion over the left lower lobe of the lung was noted on lung computerized tomography scan. Subsequent bronchoscopic biopsy proved metastatic ACC. A positron emission tomography (PET) scan detected fluorodeoxyglucose (FDG)-avid lesions in the right mastoid, left occipital regions, right clavicle, upper cervical spine, 9th thoracic vertebra, 2nd and 4th lumbar vertebrae, right iliac bone, right proximal femoral shaft, bilateral acetabula, and left lower lobe of the lung. The patient's serum CA125 elevated to 139 units/mL and correlated with disease progression. Chemotherapy was commenced. She received one cycle of combination chemotherapy consisting of taxol (135 mg/m²) and cisplatin (60 mg/m²), but anaphylactic shock occurred in the second chemotherapy course. Taxol was replaced by taxotere. However, erythematous, well-demarcated, raised skin lesions appeared 30 minutes after the start of chemotherapy. Owing to the patient's type I allergy reaction, chemotherapy was discontinued. One month later, radiotherapy (a total of 2450 cGy over 7 fractions) to the spine lesion, right iliac fossa, and right femoral shaft was arranged for relief of bone pain. Then, palliative

chemotherapy with two courses of carboplatin and two courses of carboplatin and lipodox was arranged. Unfortunately, further disease progression, massive ascites, right chest wall and brain metastases followed, and the patient died of multiple metastases. The overall disease survival was 54 months.

Case 2

A 48-year-old married woman, gravida 4, para 3, noted right labium minor intermittent pain for the past 3 months after riding a bicycle. The patient first sought medical attention at a local hospital, and marsupialization of the right Bartholin's gland was arranged. A biopsy revealed ACC. The tumor size was about 2 cm × 2 cm × 1 cm. The patient was then referred to our hospital. Pelvic examination showed an ill-defined firm nodule over the right labia minor measuring 1.5 cm × 1.5 cm. Physical examination did not reveal other abnormalities. Chest X-ray, hematological, renal, and liver functions were all normal. The patient's serum level of CA125 was also in the normal range. The patient underwent a right hemi-vulvectomy with partial resection of the lower third of the vagina, right-side levator ani muscle and right inguinal–femoral lymph node dissection. An intraoperative frozen section was sent to the laboratory to confirm the free resection margin. Final pathology confirmed the diagnosis of ACC of Bartholin's gland with free surgical margin. There was no inguinal–femoral lymph node metastasis. No adjuvant radiation therapy was performed. One year later, owing to uterine and vaginal prolapse on the right side, total vaginal hysterectomy, bilateral salpingo-oophorectomy, sacrospinous ligament suspension, and anterior colporrhaphy were arranged. During this surgery, no tumor recurrence was found. Unfortunately, lung metastasis with bilateral multiple cotton ball lesions was found 59 months after the first operation. The patient refused further chemotherapy and took tamoxifen for 4 years with stable disease status. Dyspnea progressed, however, and she died from respiratory failure due to lung metastasis 6 months later. Overall disease survival was 120 months.

Discussion

Primary carcinoma of Bartholin's gland, first documented by Klob in 1864, is a rare malignant tumor comprising 0.001% of all female genital malignancies and 2–7% of all vulvar carcinomas [3,4]. Clinical diagnosis was established by Honan in 1897 [4,5]. It included adenocarcinoma of various types (papillary, mucinous, and colloid) and squamous cell carcinoma; 10–15% cases had ACC, which is histologically similar to the adenocarcinoma of the salivary glands.

ACC, first recognized in 1859 by Billroth, is a specific variant of adenocarcinoma of the salivary and mucous glands [4,6]. It is found in various locations such as the salivary glands, breasts, skin, and lungs. In the female genital tract, ACC is more commonly found in the cervix. The ACC of Bartholin's gland is a rare variant. Typical symptoms are similar to those of a Bartholin's gland abscess, including a painless lump in the posterior half of the vulva with or without

ulcerations and dyspareunia, abnormal bleeding, pruritus, and rarely, vulvar pain [7]. Half of the cases of carcinoma of Bartholin's gland (12 of 24) were initially clinically misdiagnosed as cysts or abscesses [8].

The clinical diagnosis of a Bartholin's gland tumor includes the tumor located in the Bartholin's gland region, overlying skin intact, tumor located deep in the labia major, normal glandular elements present on histology, areas of apparent transition from normal to neoplastic elements, histological tumor type consistent with the Bartholin's gland origin and no evidence of a previous, concurrent, or subsequent primary tumor of similar histologic type elsewhere [9]. When the tumor progresses, the overlying skin may become ulcerated [4]. Owing to the limited number of cases, it is difficult to identify the risk factors of ACC of Bartholin's gland, but pregnancy may be a factor.

Microscopically, ACC of Bartholin's gland exhibits the classic "cribriform" adenoid cystic pattern, characterized by anastomosing cords of cells, often surrounding acellular spaces. The acellular area contains variable amounts of mucin and hyalinized material. In addition, solid cellular and tubuloglandular patterns of similar cell types are present. The tumor cells, small and basaloid, have regular nuclei and little cytoplasm. In addition, there may be residual normal Bartholin's gland elements with areas suggestive of transition into neoplastic tissue [9]. The infiltration of perineural spaces is another main microscopic feature of this type of tumor (Figs. 1 and 2). Thus, many patients experience itching and burning sensations before a mass becomes palpable at physical examination [2,10].

The ACC of Bartholin's gland is a slow-growing tumor with late clinical presentation of recurrence and distant metastasis. According to Copeland et al., the 5-year progression-free interval is 47% and the 5-year survival rate is 71%. The progression-free intervals and survival rates are 38% and 50% at 10 years, and 13% and 51% at 15 years, respectively [9]. From these results, 5-, 10-, and 15-year progression-free survival interval rates rather than 5-year survival rates for ACC of Bartholin's gland are recommended.

There is currently no consensus regarding the optimal surgical treatment for ACC of Bartholin's gland. Both simple

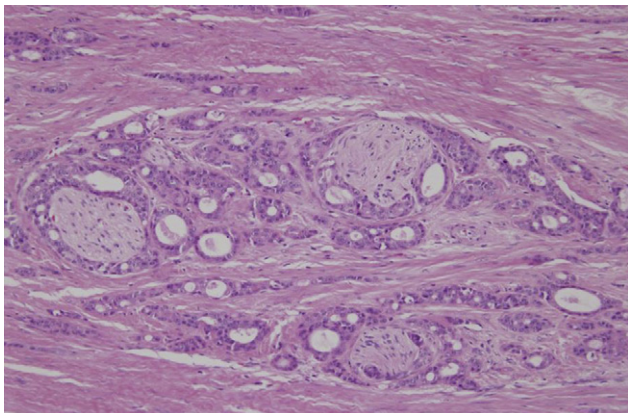


Fig. 1. H&E stain (200×). Perineural invasion of atypical cribriform glands.

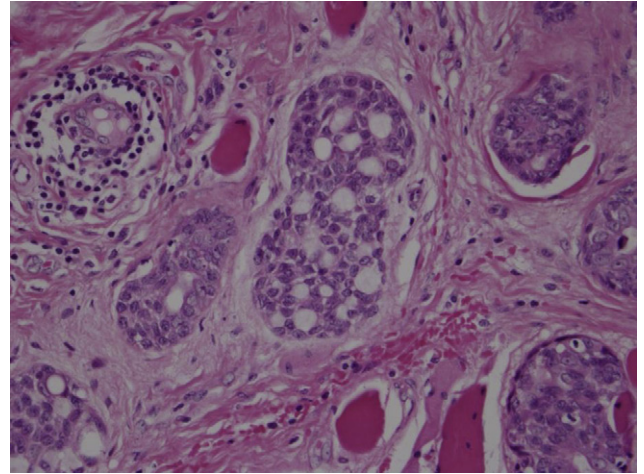


Fig. 2. H&E stain (400×). Tumor cells are of low grade with only mild cytologic atypia and small nucleoli. This characteristic is compatible with the notorious feature of adenoid cystic carcinoma. Low-grade cytologic abnormalities with advanced infiltrative growth pattern are shown.

excision and radical vulvectomy with or without lymph node dissection have been performed. According to the experience of Lelle et al, if an adequate surgical margin can be achieved, a more conservative surgical procedure with adjuvant radiation may be reasonable [11]. According to the review by Yang et al, 68.9% of patients who had a simple excision had recurrences compared with 42.9% of patients who had a radical vulvectomy. Although the information on the status of margins at the initial surgery was incomplete, the positivity of resection margin was 48% in the simple excision group and 30% in the radical vulvectomy group [12]. Following the review of Yang et al, we included the new cases reported in the last 5 years and conducted a new review of surgical intervention (Table 1) [13,14]. Radical vulvectomy can reduce local recurrence, but it has no impact on distant metastasis.

Adjuvant radiation does lower the incidence of local recurrence in patients with positive resection margins. Rosenberg et al and Copeland et al reported the benefits of postoperative external beam radiation for patients with positive margin.[9,15]. In the literature, 16 patients received adjuvant radiotherapy, the 10 patients with positive resection margins did not have local recurrence, but six of them developed distant metastasis (Table 1).

With regard to primary radiation or concurrent chemoradiation, Lopez-Varela et al conducted a study at Massachusetts General Hospital (MGH) about primary treatment of Bartholin's gland carcinoma with radiation or chemoradiation. The median follow-up was 87.2 months (45–142). Three- and 5-year survival rates were 71.5% and 66%, respectively, and were comparable with outcomes after surgery and postoperative radiation therapy. The authors conclude that primary radiation or chemoradiation therapy offers an effective alternative to surgery with preservation of genital function and low morbidity [16].

The clinical course of ACC of Bartholin's gland appears to be different from that of adenocarcinoma and squamous cell carcinoma of Bartholin's gland. Metastatic disease to the

Table 1
Adenoid cystic carcinoma of Bartholin's gland: primary treatment, resection margins, and recurrence.

Treatment	Positive resection margin	Recurrence	Local recurrence	Distant metastasis
Primary treatment	—	—	—	—
Simple excision (<i>n</i> = 35)	13 (48.1%), NM, 8	21(67.7%), NM, 4	17 (54.8%)	10 (32.3%) (4, lung; 3, bone; 1, mediastinum)
Radical vulvectomy (<i>n</i> = 32)	7 (31.8%), NM, 10	14 (46.7%), NM, 2	4 (13.3%)	11 (36.7%) (8, lung; 5, bone; 1, skull; 1, brain; 1, liver)
Adjuvant treatment	—	—	—	—
Radiotherapy (<i>n</i> = 16)	10 (66.7%), NM, 1	6 (40.0%), NM, 1	0 (0%)	6 (40%) (6, lung; 3, bone; 1, liver; 1, brain)

NM = not mentioned.

inguinal femoral nodes is uncommon. It may be via a hematogenous route. The most common metastatic site is the lung [4,12,17,18]. In the review by Bernstein et al. [3], five of 20 patients died from lung metastasis 4–23 years after initial treatment. Yang et al used six cycles of cyclophosphamide, Adriamycin, and cisplatin for one patient with lung metastasis, achieving only stable disease status [12]. According to a review of chemotherapy for ACC of the head and neck, the response rates to chemotherapy are low and the response duration is generally short. No standard chemotherapy regimen was recommended [19].

We treated our patient (Case 2) with tamoxifen for 4 years and achieved stable disease status. According to Copeland et al, seven of 14 patients aged below 42 years had their adenoid cystic vulvar tumor diagnosed in association with pregnancy [9]. Dramatic hormonal change may induce cancer, and hormone therapy may play a role in the treatment of ACC of Bartholin's gland. We used antiestrogen therapy owing to the strong relation between pregnancy and this tumor, as mentioned in Copeland's review series [9]. Clearly, further studies on hormone therapy are required.

References

- [1] Budd GT, Groppe CW. Adenoid cystic carcinoma of the salivary gland. Sustained complete response to chemotherapy. *Cancer* 1983;51:589–90.
- [2] Anaf V, Buxant F, Rodesch F, Simon P, van de Stadt J, Noel JC, et al. Adenoid cystic carcinoma of Bartholin's gland: what is the optimal approach? *Eur J Surg Oncol* 1999;25:406–9.
- [3] Klob JM. *Pathologische Anatomie der Weiblichen Sexualorgane* Wein; 1864.
- [4] Bernstein SG, Voet RL, Lifshitz S, Buchsbaum HJ. Adenoid cystic carcinoma of Bartholin's gland. Case report and review of the literature. *Am J Obstet Gynecol* 1983;147:385–90.
- [5] Honan JH. Inaugural dissertation. Berlin; 1879.
- [6] Billroth T. Beobachtungen über Geschwulste der Speicheldrüsen, *Virchows Arch. Pathol Anat* 1859;17:357.
- [7] Finan MA, Barre G. Bartholin's gland carcinoma, malignant melanoma and other rare tumours of the vulva. *Best Pract Res Clin Obstet Gynaecol* 2003;17:609–33.
- [8] Chamlian DL, Taylor HB. Primary carcinoma of Bartholin's gland. A report of 24 patients. *Obstet Gynecol* 1972;39:489–94.
- [9] Copeland LJ, Sneige N, Gershenson DM, Saul PB, Stringer CA, Seski JC. Adenoid cystic carcinoma of Bartholin gland. *Obstet Gynecol* 1986;67:115–20.
- [10] DePasquale SE, McGuinness TB, Mangan CE, Husson M, Woodland MB. Adenoid cystic carcinoma of Bartholin's gland: a review of the literature and report of a patient. *Gynecol Oncol* 1996;61:122–5.
- [11] Lelle RJ, Davis KP, Roberts JA. Adenoid cystic carcinoma of the Bartholin's gland: The University of Michigan experience. *Int J Gynecol Cancer* 1994;4:145–9.
- [12] Yang SY, Lee JW, Kim WS, Jung KL, Lee SJ, Lee JH, et al. Adenoid cystic carcinoma of the Bartholin's gland: report of two cases and review of the literature. *Gynecol Oncol* 2006;100:422–5.
- [13] Wang X, Lu W, Zhu C, Ye F, Xie X. Adenoid cystic carcinoma of Bartholin's gland with lung metastasis: a case report. *Eur J Gynaecol Oncol* 2009;30:317–20.
- [14] Korkontzelos I, Fragkoulidis M, Stavroulis A, Apostolikas N, Terzakis E. Adenoid cystic carcinoma of the Bartholin's gland in a young patient: eight-year follow-up. *Eur J Gynaecol Oncol* 2009;30:686–8.
- [15] Rosenberg P, Simonsen E, Risberg B. Adenoid cystic carcinoma of Bartholin's gland: a report of five new cases treated with surgery and radiotherapy. *Gynecol Oncol* 1989;34:145–7.
- [16] Lopez-Varela E, Oliva E, McIntyre JF, Fuller Jr AF. Primary treatment of Bartholin's gland carcinoma with radiation and chemoradiation: a report on ten consecutive cases. *Int J Gynecol Cancer* 2007;17:661–7.
- [17] Abrao FS, Marques AF, Marziona F, Abrao MS, Uchoa Junqueira LC, Torloni H. Adenoid cystic carcinoma of Bartholin's gland: review of the literature and report of two cases. *J Surg Oncol* 1985;30:132–7.
- [18] Anderson RJ, Johnston WW, Szpak CA. Fine needle aspiration of adenoid cystic carcinoma metastatic to the lung. Cytologic features and differential diagnosis. *Acta Cytol* 1985;29:527–32.
- [19] Papaspyrou G, Hoch S, Rinaldo A, Rodrigo JP, Takes RP, van Herpen C, et al. Chemotherapy and targeted therapy in adenoid cystic carcinoma of the head and neck: a review. *Head Neck* 2011;33:905–11.