Surgical Treatment for Locally Advanced Adenoid Cystic Carcinoma of the Bartholin's Gland: A Case Report

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Adenoid cystic carcinoma (ACC) of the Bartholin's gland (BACC) is an extremely rare malignancy of the vulva. The characteristics of BACC include slow tumor growth and aggressive invasion, especially with perineural involvement. A 64-year-old Japanese woman complained of a mass and pain in the perineum. A 3 cm-sized mass was palpated inside of the labia majora. Diagnostic imaging demonstrated the tumor invading the anus and urethra. The patient underwent total pelvic exenteration with radical vulvectomy. Pathological findings revealed that the tumor was BACC. The surgical margin was positive for tumor cells, which necessitated adjuvant radiotherapy. No serious complications were associated with the surgery and radiotherapy. There is no clear consensus on to the proper surgical intervention in BACC. Achieving tumor-free surgical margins is desired to avoid recurrence. However, such attempts have often failed in reported BACC cases with extended surgical resection. Nevertheless, given the aggressive nature of BACC, extensive surgery including total pelvic exenteration is justified, particularly with promising reported efficacy of adjuvant radiotherapy on BACC prognosis.

Key words: adenoid cystic carcinoma, Bartholin's gland, total pelvic exenteration

INTRODUCTION

Adenoid cystic carcinoma (ACC) of the Bartholin's gland (BACC) is an extremely rare malignancy [1]. ACC accounts for $<1\%$ of all lower female genital tract malignancies, and is thought to originate from the Bartholin's gland of the vulva and the uterine cervix [1, 2]. A very small portion (0.1–0.7%) of all vulvar carcinomas are of Bartholin's gland origin, and ACC constitutes 10–30% of all Bartholin's gland malignancies [1–3]. BACC shares most clinical and histopathological features with ACC of other sites (e.g., the salivary gland) [4]. Thus, BACC typically exhibits slow growth, frequent local recurrence (likely due to its invasive nature into perineural areas), and a relentless clinical course usually with a fatal outcome [2].

The rarity of BACC contributes to the lack of both randomized control studies and retrospective studies including a large number of cases, and no consensus has been achieved with respect to a standard therapeutic strategy. Nevertheless, in most cases with rather early-stage BACC, either a simple excision or radical vulvectomy with or without lymphadenectomy is performed as a first-line treatment [5–8], and adjuvant radiation therapy is offered when there is an increased chance of local recurrence such as positive surgical margins [5, 9]. However, patients presenting with locally advanced BACC remain a therapeutic challenge. In this report, such a case of BACC requiring total pelvic exenteration is described, with a review of the literature included.

CASE REPORT

A 64-year-old Japanese woman (G2P2) presented to our institution with two months of perineal pain. She had been feeling a lump in the left perineum for 4 years. On digital examination, a 3 cm-sized hard mass was palpable within the left vulvar Bartholin's gland area. The mass was not remarkable by visual inspection. The vaginal mucosa and perineal skin appeared normal. The mass was biopsied and the histology revealed carcinoma with myoepithelial components. Neoplastic cells with mildly enlarged nuclei were noted, and these cells formed irregular papillary or tubular structures. Some of the latter structures comprised two layers of tumor cells. Perineural invasion was not evident. Immunohistochemical staining revealed that the outer-layer cells of tubular structures were positive for p63 and smooth muscle actin (SMA) indicating differentiation to myoepithelial cells. T1-weighted magnetic resonance imaging (MRI) showed a 4×3 cm-sized tumor that possessed a characteristic of highly invasive cancers, with blurred margins reaching the anus and urethra. The lateral margins of the tumor were irregular, but normal appearing adipose tissue and superficial transverse perineal muscle were seen between the tumor and the inferior pubic ramus (Fig. 1A). Contrast enhanced computed tomography (CT) showed that the tumor had an abscess-like appearance with an enhanced ring (Fig. 1B). Metastasis to distant organs or lymph nodes was not detected. With a preoperative diagnosis of International Federation

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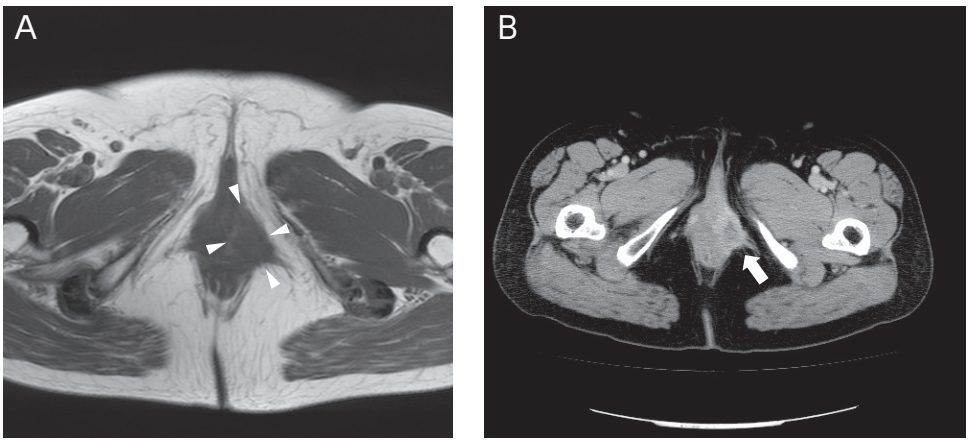

Fig. 1 A: T1-weighted MRI showing a 4 × 3 cm-sized tumor with blurred margins reaching the anus and urethra (*arrow heads*), irregular lateral margins of the tumor, and normal appearing adipose tissue and superficial transverse perineal muscle between the tumor and the inferior pubic ramus.
B: Contrast-enhanced CT demonstrating an abscess-like appearance with an enhanced ring (*arrow*).

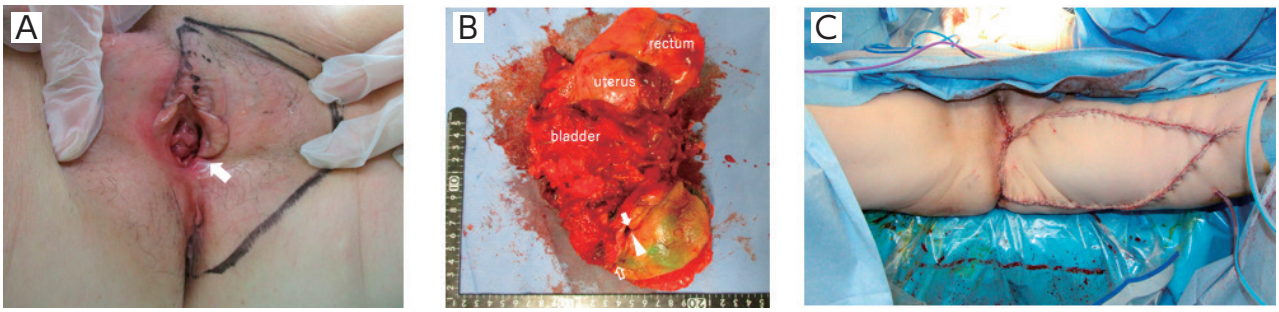

Fig. 2 A: Markings for the skin incision line are shown. An approximately 3 cm-sized hard mass (*arrow*) was palpable within the left vulvar Bartholin's gland area. The skin incision line coursed along the upper margin of the clitoris and the lower margin of the inferior pubic ramus, then continued downward while maintaining a 5-cm distance from the left labia majora, and extended 3 cm below the anus.
B: The vulvar tumor with the rectum, anus, perineum, bladder, urethra, lower ureters, and internal reproductive organs was removed en block. *Arrow head*, location of tumor. *Closed arrow*, vaginal inlet. *Open arrow*, anus.
C: Vulvar reconstruction was performed with a gracilis myocutaneous flap.

of Gynecology and Obstetrics (FIGO) stage II vulvar cancer, the patient underwent total pelvic exenteration with radical vulvectomy, left inguinal lymphadenectomy, and bilateral pelvic lymphadenectomy.

The surgery was performed by a multidisciplinary team including two gynecologists, two urologist, and two plastic surgeons in the following order: 1) left inguinal and bilateral pelvic lymphadenectomy, 2) ureteral mobilization and dissection at the crossing point of the uterine artery, 3) rectal transection at the rectosigmoid junction, 4) mesorectal plane dissection to the level of the levators, 5) complete detachment of the ventral, lateral, and dorsal parametria, 6) mobilization of the bladder from the pelvic wall, 7) endopelvic fascia and levator ani muscle resection, 8) perineal resection (radical vulvectomy), 9) vulvar reconstruction, and 10) diversion of visceral functions.

Radical vulvectomy was performed with an incision line determined as shown in Fig. 2A. After the en bloc removal of the rectum, anus, perineum, bladder, urethra, lower ureters, and internal reproductive organs (Fig. 2B), vulvar reconstruction was performed with a gracilis myocutaneous flap (Fig. 2C). An ileal conduit for urinary diversion and a descending colostomy were created, and a J-shaped omental flap was placed into position over the pelvic floor defect.

Total surgical time was 11 hours and 4 minutes. Blood loss during surgery was 700 mL and autologous blood transfusion (300 mL of her own red blood cells) was performed. The surgery was otherwise uneventful.

Macroscopic examination demonstrated a vulvar tumor of 36 × 24 × 38 mm in size that involved the anus and urethra (Fig. 2B). Microscopic examination found that atypical cells with nuclear enlargement and prominent nucleoli formed gland-like and papillary structures. The gland-like structures were surrounded by tumor cells with clear cytoplasm that formed two layers. In some areas, tumor cells proliferated in a cribriform or solid pattern (Fig. 3A). Vascular and perineural invasions were also noted (Fig. 3B). At the periphery of the tumor, cells migrated in a scattered fashion and infiltrated the urethra, parametrium close to the cervix, and adipose tissue far from the main tumor mass. The surgical margins were positive for tumor cells in two out of 38 surgical specimens examined. Two such specimens came from tissue originally located just beneath the inferior pubic ramus, more than 5 cm away from the main tumor. No metastasis was found in inguinal and pelvic lymph nodes (0/52). Immunohistochemical staining demonstrated that the

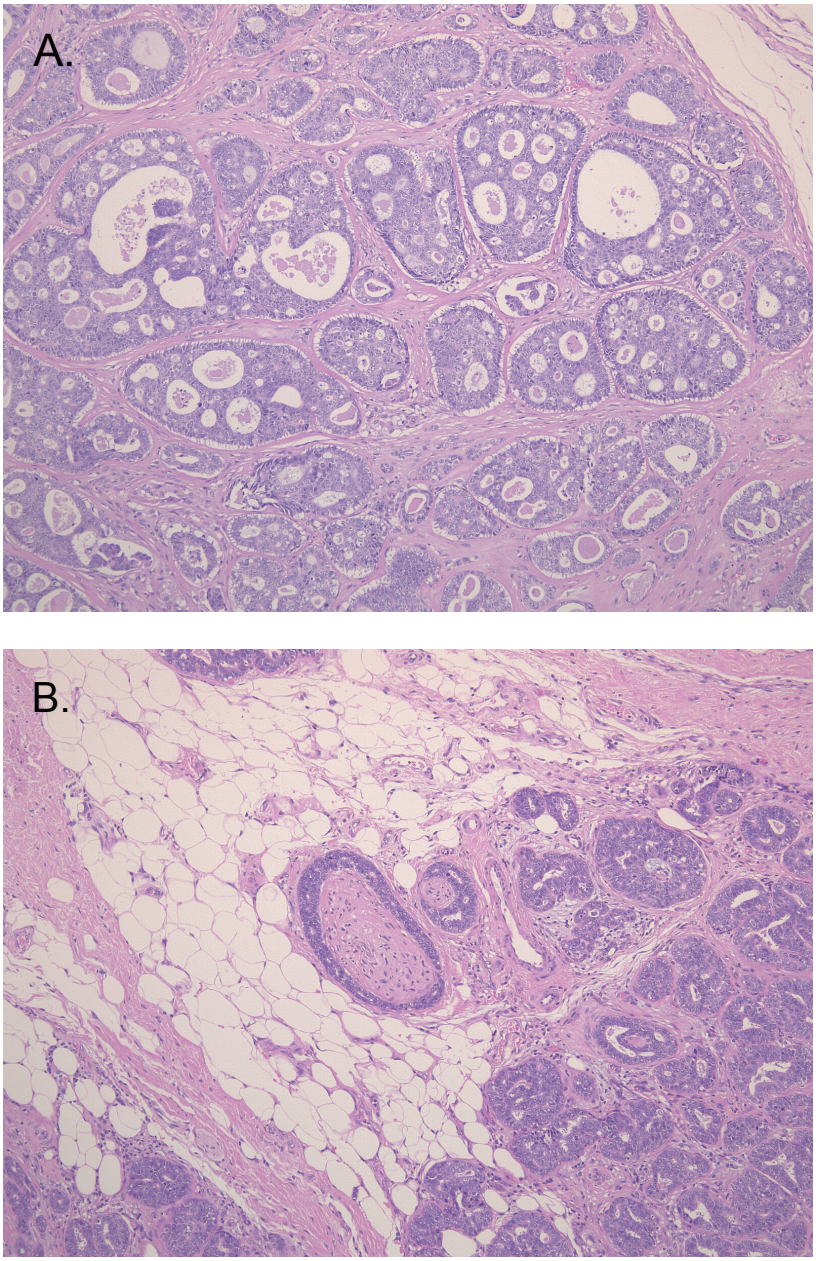

Fig. 3 A: Microscopic findings showing tumor cells forming cribriform and gland-like patterns (HE stain, × 100 magnification).
B: Perineural invasion neighboring the cribriform nests of tumor cells (HE stain, × 100 magnification).

cells forming gland-like structures were positive for cytokeratin (AE1/AE3). The outer-layer cells of the bilayer structures were positive for known markers of myoepithelial cells including vimentin, p63, smooth muscle actin (SMA), and S-100. C-kit was strongly positive and Ki-67 staining was positive in 20–30% of cells in the cribriform nests. Thus, these histopathological features were compatible with ACC [1].

The patient was diagnosed as having stage IV vulvar cancer (adenoid cystic carcinoma; pT3N0M0) according to the FIGO classification. Given the positive surgical margin, adjuvant radiotherapy with 5940 cGy was performed. The patient had no major postsurgical complications including surgical site infection or bowel/urinary complications (e.g., fistula and stoma failure). Bed rest for one week was needed for wound healing. She underwent inpatient rehabilitation for walking recovery and education for the ileal conduit and colostomy. She was discharged home 35 days after the surgery. At her last visit 6 months after the surgery, the patient was recovering well without any evidence of recurrence.

DISCUSSION

This report describes a 64-year-old female patient diagnosed with advanced BACC (FIGO stage IV). BACC was described for the first time in 1859 by Billroth [10]. To date, approximately 100 cases of BACC have been reported [3–23]. In addition, a recent study describes the clinicopathological features and survival outcomes of all registered patients (n = 70) with BACC from 1973 to 2014, using the population-based cancer registry database, provided by the National Cancer Institute, which covers up to 28% of the United States population [2]. Advanced age and stage were significantly associated with a worse prog-

nosis in patients with BACC. The distribution of BACC patients in stage I, II, III, and IV was 52.7%, 14.5%, 25.5%, and 7.3%, respectively, indicating a tendency for BACC patients to have higher disease stage. The median age of patients with BACC was 59 years (range, 31–95 years) [2]. In a review of 79 cases reported up to 2011, the median age of BACC patients was 48 years (range, 25–80 years) [3]. Thus, BACC tends to occur over a wide age range compared to other types of Bartholin's gland carcinoma or vulvar carcinoma that occur predominantly in elderly women [1]. The 5-year cause-specific survival and overall survival rates were 88% and 81%, respectively [2]. BACC is a slow-growing tumor with frequent local recurrence. The rate of distant metastasis (usually, lung [15, 16] and bone) is estimated to be 31% [7]; metastasis often occurs a long time after the initial diagnosis of BACC. Patients may continue to live for an extended period after an initial recurrence, although the disease is typically relentless in its clinical course. Copeland *et al.* describe the progression free interval as 47% at 5 years and 38% at 10 years, while the overall survival rate was 71% and 59% at 5 and 10 years, respectively [7].

BACC shares histological characteristics with ACC of the salivary gland [4]. ACC consists of epithelial and myoepithelial cells that can manifest a variety of tubular and cribriform structures with variably solid components. The most typical and recognizable architectural form is the cribriform pattern, which is characterized by nests of tumor cells interrupted by sharply punched-out spaces filled with basophilic basement membrane material [1, 24]. A distinctive feature of the tubular pattern is haphazard proliferation of tubular structures frequently lined by two layers of tumor cells [12]. In ACC, mitoses are not commonly seen and perineural invasion is almost invariably observed. Tumor cells around pseudocysts show immunoreactivity for SMA, p63, and S-100, suggesting myoepithelial differentiation. The lumen of the pseudocyst demonstrates intense immunoreactivity for cytokeratins (AE1/AE3 and CK8/18) and c-KIT/CD117 [1]. Thus, in the present case, the histopathological features were compatible with those of ACC.

The symptoms of BACC include a painless mass in the posterior half of the vulva with or without ulceration, dyspareunia, hemorrhage, and pruritus [8]. Early-stage patients may experience itching and burning before a tumor becomes palpable, probably due to BACC's strong tendency of perineural invasion [13]. The current case presented with perineal pain. However, presentation in the form of pain is rare [8, 13]. This may be explained by the fact that the patient had a locally advanced disease.

A standard therapy for BACC has not been established due to the rarity of this tumor. However, in most cases of BACC in the literature, surgical resection was performed with or without inguinal lymphadenectomy [5–8]. The therapeutic and prognostic roles of inguinal lymphadenectomy are unclear since inguinal lymph node metastasis is rare [5]. Obtaining negative surgical margins is ideal; therefore more extensive resection may well be justified. To support this notion, patients with radical vulvectomy have a lower recurrence rate than those with simple excision [3, 4, 8, 23]. In a review by Alsan *et al* [3], recurrence was observed in 35% of cases with positive resection margins and in 10% of those with negative resection margins. Nevertheless, difficulties in achieving tumor-free surgical margins have been reported. Surgical margins were positive in 48% of patients who underwent excision of the involved vulva, and 30% of those who underwent radical vulvectomy [3], most probably reflecting the aggressive and highly invasive nature of BACC. Several reports support the benefit of adjuvant radiotherapy for BACC patients with positive surgical margins [7, 11, 23]. In a review by Hsu *et al*, out of 16 surgical-margin positive cases treated with adjuvant radiotherapy, 10 patients did not have local recurrence, whereas 6 patients developed distant metastasis [23], suggesting a beneficial role for adjuvant radiotherapy at least in reducing local recurrence. Based on these reports, the present patient underwent adjuvant radiotherapy.

As for advanced disease, planning a therapeutic strategy poses an even greater challenge for the physician. Pelvic exenteration may be an option for treatment of locally advanced BACC cases to obtain negative resection margins. Including this instance, only 6 cases of pelvic exenteration (posterior or total) have been reported in the literature [4, 13, 21, 22, 25]. Among the 5 previously reported cases, at least three achieved complete resection. Unfortunately, in the present case complete resection was not achieved, with two positive surgical margins found in 38 surgical specimens examined. These two specimens came from tissue more than 5 cm away from the main tumor, again indicating the highly invasive nature of this cancer. Similarly, microscopic invasion far from the main tumor is often observed in patients with ACC originating from the head and neck [26].

Because the risk of associated morbidities as well as the psychosexual impact of pelvic exenteration is very high, radiation therapy followed by no surgery or less radical surgery may emerge as an alternative to pelvic exenteration [7, 27]. It has not been determined whether primary radiotherapy and concurrent chemo-radiotherapy are viable alternatives to primary surgical intervention for BACC. To date, only one study has been reported. Lopez-Varela *et al.* retrospectively reviewed their 10 consecutive cases of Bartholin's gland carcinoma primarily treated with radiation or chemoradiation [14]. The median follow-up was 87.2 months (45–142) and 5-year survival rate was 66%, which matches outcomes shown after surgery with postoperative radiation therapy. However, only two cases of BACC were included in the study. One of these patients died of a non-related disease after only 4 months and the other had lung metastasis after 3.7 years, developed local recurrence after 4.5 years, and died of the disease after 11.8 years [14]. Similarly, no conclusions are available on the roles of neoadjuvant and/or primary chemotherapy for BACC. According to a review of chemotherapy for ACC of the head and neck, the response rates to chemotherapy are low, the response duration is generally short, and there are no standard chemotherapy regimens [28]. Thus, for now, a surgery-first approach should be the therapeutic strategy of choice for BACC until solid evidence is provided otherwise. For locally advanced BACC, performing extensive surgery including total pelvic exenteration is justified when the locally aggressive nature of BACC

and the reported promising efficacy of adjuvant radiotherapy on prognosis are considered [7, 11, 23].

Thus, locally advanced BACC remains a therapeutic challenge. Clinical case reports support a surgery-first approach for this extremely rare, slow-glowing carcinoma of the vulva with frequent recurrence. Because of the non-availability of large or randomized studies, an individually tailored approach should be taken based on up-to-date knowledge of BACC. Before performing extensive surgery such as pelvic exenteration, operability should be judiciously determined and a careful informed consent process with the patient and family is mandatory. In addition, given the slow-growing but relentless clinical course and worsening prognosis associated with increased clinical stage, early diagnosis and therapy is essential. The physician should keep in mind that BACC can occur over a wide age range and perform a biopsy of a cyst or mass in the Bartholin's gland when a presumed diagnosis as benign is in doubt.

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