

Case Reports

Neoadjuvant chemoradiotherapy followed by radical vulvectomy for adenoid cystic carcinoma of Bartholin's gland: a case report and review of the literature

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Summary

Adenoid cystic carcinoma (ACC) of Bartholin's gland is a rare variant and around 90 cases have been reported. Herein, the authors report a locally advanced ACC of Bartholin's gland that was treated with neoadjuvant chemotherapy followed by right radical hemi-vulvectomy and reconstruction with a gracilis musculocutaneous flap. There was no evidence of recurrence after three years of follow up.

Key words: Adenoid cystic carcinoma; Bartholin's gland; Neoadjuvant; Vulvar carcinoma.

Introduction

In the United States, carcinoma of the vulva accounts for 5% of all gynecological malignancies [1]. Primary carcinoma of the Bartholin's gland accounts for 2-7% of all malignant vulvar tumors [2]. Adenoid cystic carcinoma (ACC) of Bartholin's gland is a rare variant and around 90 cases have been reported in the literature [3-9]. It is characterized by indolent growth, perineural infiltration, local invasion and blood-borne metastasis. There is no consensus regarding the optimal treatment. Herein, the authors present a case of locally advanced ACC of Bartholin's gland that was managed by neoadjuvant chemo-radiation followed by radical hemi-vulvectomy with relevant literature review.

Case Report

The present patient is 52-years-old G4P1 and without any prior significant medical history. She has had regular and normal Pap tests. Menopause was at age 51 and she did not have hormonal replacement treatment. In May 2011, one month prior to seeking medical advice, she had external dyspareunia and was concerned about a right vulvar lump that had increased in size over time. She did not notice rectal bleeding or hematuria. Her gynecologist detected a right posterior vulvar mass measuring 7 x 8 cm and he performed a fine needle aspiration. The cytological analysis showed neoplastic basaloid cells with cribriform architecture suggestive of ACC of Bartholin's gland. She was referred to the present center for further management. Clinical examination, re-

vealed no enlarged lymph nodes. The uterus and the adnexa were normal. The authors noticed a 10 x 8 cm firm and tender mass occupying the right posterior vulva. It extended anteriorly to the right labia majora, cranially to the mid-vaginal wall level and postero-laterally into the ischio-rectal fossa. The overlying skin was normal and there was no obvious vaginal, anal or rectal invasion. However, the mass was in close proximity to these structures. Tru-cut biopsy was performed and the pathology revealed a nest of cord and trabecula of cuboidal basaloid neoplastic cells with high nuclear to cytoplasm ratio, in a fibrotic stroma. The tumor cells frequently form a cribriform pattern and an amorphous hyaline basement membrane-like material within the acini and palisading pattern on periphery (Figure 1A-B).

MRI of the pelvis demonstrated a complex oval-shaped heterogeneous mass measuring 10.1 x 5.5 x 7.2 cm located in the right perineal region. The mass was abutting the posterior and inferior portion of the vagina and right anal wall without evidence of direct invasion. The mass had two major components on MRI. The posterior portion demonstrated increased signal intensity on T1-weighted sequences and moderate to high T2 signal intensity with no enhancement following gadolinium administration whereas the anterior and central component demonstrated isointense signal on T1-weighted sequences and slight hyperintense T2 signal with moderate enhancement following gadolinium administration (Figure 2). There was no pelvic or inguinal adenopathy or ascites. CT scan of the chest and pelvis did not suggest any distant metastasis. PET-CT revealed a heterogeneous hyper-metabolic mass with the highest uptake in the right anterior and superior aspect of the mass. No distant metastasis was suspected.

Due to the size and proximity of the tumor to the anus and the rectum, neoadjuvant chemo-radiation was recommended by the

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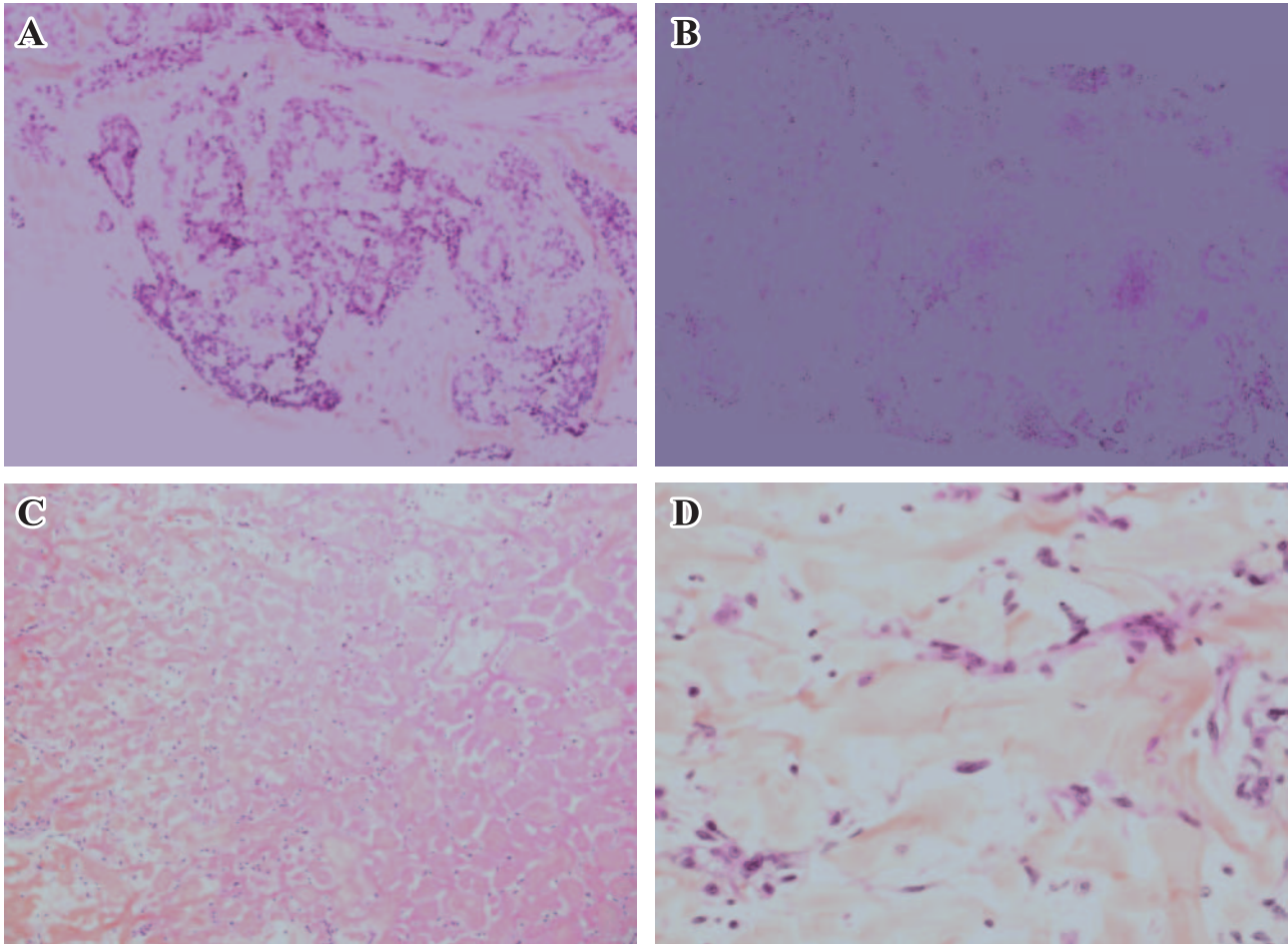


Figure 1. — A: (Pre-chemotherapy) The biopsy shows nest of trabecula and cords of basaloid cells in a fibrotic stromal background and amorphous hyaline material. B: (Pre-chemotherapy) The higher magnification shows cribriform and trabecular pattern of basaloid tumor cells forming acini or microcyst and central eosinophilic material. C: (Post-chemotherapy) demonstrate individual cells in a background of highly hyalinized stroma. D: Neoplastic cells with chemotherapy effect show round to epithelioid cells with round nuclei, basophilic nucleoli, smoggy chromatin, and vacuolar cytoplasm.

tumor board to avoid posterior exenteration. She had weekly cisplatin 40 mg/m² for total of six cycles concurrently with radiotherapy. IMRT technique was used at a dose of 45 Gy over 25 fractions to the inguinal LND and pelvis and boost of 50 Gy over 25 fractions at the primary tumor. MRI of the pelvis was done after she had received 45 Gy to evaluate response. The size of the tumor decreased partially to 10.7 x 5.8 x 5.1 cm. Due to poor response, the dose to the primary tumor was increased to total of 60 Gy over total duration of 45 days. Apart from grade 3 dermatitis, the treatment was well-tolerated.

Examination under GA was done to plan the surgical treatment. The authors detected an indurated mass measuring 8 x 5 cm that extended superiorly to the level of mid-vagina and postero-laterally to the right ischiorectal fossa. The skin overlying the tumor was normal and there was no evidence of vaginal, rectal or anal invasion. The patient underwent right radical vulvectomy. Multiple frozen sections at the tumor bed were negative. The defect was reconstructed with a gracilis musculocutaneous flap.

The post chemotherapy specimen demonstrated a lesion measuring 8 x 5 x 5 cm situated 0.1 mm from the margin, demonstrating mainly cribriform and trabecular pattern with hyalinized

stroma and variable sized cysts with amphophilic to eosinophilic cytoplasm with perineural and without lymphovascular invasion. The chemotherapy effects revealed as an abundant hyalinized stroma with lacunar or trabecular pattern of tumor cell distribution. The neoplastic cells show large nuclei with smoggy chromatin and abundant vacuolar cytoplasm (Figures 1C-D). Biopsies of the tumor bed were negative.

During the postoperative period, the skin over the flap necrosed and the wound was managed with debridement and vacuum assisted closure (VAC). Complete healing occurred within four months. She has been followed up with interval MRIs and there was no evidence of recurrence after three-years of follow-up.

Discussion

Carcinoma of Bartholin's gland was described first by Klob in 1864. The initial clinical diagnostic criteria were established by Honan and were revised by Copeland *et al.* [10]. The median age at the time of diagnosis is 48 years.



Figure 2. — Coronal T2-weighted image of the pelvis demonstrating a complex oval-shaped heterogeneous mass measuring 10 x 5 x 7 cm occupying the right ischio-rectal fossa and abutting the posterior and inferior portion of the vagina and right anal wall without evidence of direct invasion.

The chief clinical complaints are pain and burning sensation associated with mass in the vulva. The duration of symptoms before seeking medical advice ranges from three months to two years [3]. Often, there is a doctor's delay due to initial misdiagnosis as Bartholin's cyst, which is often treated by drainage or marsupialization. It is suggested that enlargement of Bartholin's gland in women older than 40 years old should be considered malignant until proven otherwise. Few cases were diagnosed by fine needle aspiration [11]. However, the diagnosis is usually made postoperatively after resection. ACC of Bartholin's gland usually share similar histological manifestation with upper respiratory tract or salivary gland tumors. The tumor manifests mainly in cribriform, trabecular or solid pattern. The cribriform type usually presents with pseudo-cystic areas filled by hyaline and eosinophilic material consists of glycosaminoglycan and PAS and Alcian blue reactive reduplicated basement membrane and is most often associated with perineural invasion. The cells show high nuclear to cytoplasmic ratio and peg-shaped nuclei [12]. The differential diagnosis includes adenocarcinoma, small cell carcinoma (primary and metastatic), small cell squamous cell carcinoma, and basal cell carcinoma.

There are no consensus regarding the optimal treatment. Radical vulvectomy and simple excision with or without inguino-femoral lymphadenectomy were commonly applied. Negative resection margin was achieved in 70% by radical vulvectomy versus 52% by simple excision [13]. The value of lymph node dissection is obscure. Five cases have been reported so far with metastasis to inguinal lymph nodes out of 38 lymph node dissections [6, 8, 14-16]. Adjuvant radio-

therapy is recommended if the surgical resection margins are positive or perineural invasion is identified. Local recurrence rate was 9.5% after adjuvant radiotherapy versus 37.5% for those who did not receive adjuvant radiation [3]. Despite the excellent loco-regional control, 30% of the patients developed distant metastasis. Lung and bone are the most common sites of metastasis [13].

Primary radiotherapy of ACC of Bartholin's gland was the modality of treatment in only two patients [17]. Both had initial complete response. One patient died after four months from intercurrent disease and the other suffered from local and distant metastasis three years after the initial treatment and succumbed to her disease. In the present case, the tumor was in closed proximity to the anus and the rectum, which preclude achieving negative resection margins without posterior exenteration. To avoid complications and psychosexual impact associated with exenteration on a young patient, the authors opted to neoadjuvant chemo-radiation.

To the authors' knowledge, this is the first case reported of neoadjuvant chemo-radiation in ACC of Bartholin's gland. In ACC of the head and neck, carboplatin and paclitaxel were given concurrently with radiation, which was effective in achieving local control and organ preservation [15]. In metastatic or local recurrent ACC of the head and neck, cisplatin is the most active single agent and CAP regimen is the most active combination regimen [16]. On these bases the authors chose cisplatin as the neoadjuvant regimen of choice. Despite the high dose of radiation, the tumor only decreased partially in size. However, they were successful in their goal and preserved her organs. The margin of the resected tumor was positive. However, multiple biopsies at the tumor beds including the site corresponding to that positive margin were negative.

In summary, ACC of Bartholin's gland is a rare malignancy of the vulva and it is characterized by indolent growth, local invasion, and late distant recurrence. Primary treatment should be radical resection. Inguinal lymphadenectomy should be reserved for patients with either clinically or radiological suspicious lymph nodes for metastasis. Patients with positive margins should have adjuvant radiotherapy to reduce the risk of local recurrence.

Neoadjuvant radiotherapy with weekly cisplatin did not significantly reduce the tumor size. Other chemotherapy regimens combined to radiotherapy might yield better results.

References

- [1] American Cancer Society: "Cancer Facts and Figures 2012". Atlanta GACS. 2012. Available at: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf>
- [2] Cardosi R.J., Speights A., Fiorica J.V., Grendys E.C., Jr., Hakam A., Hoffman M.S.: "Bartholin's gland carcinoma: a 15-year experience". *Gynecol. Oncol.*, 2001, 82, 247.

- [3] Alsan C.I., Vinh-Hung V., Eren F., Abacioglu U.: "Adenoid cystic carcinoma of the Bartholin's gland: case report and systematic review of the literature". *Eur. J. Gynaecol. Oncol.*, 2011, 32, 567.
- [4] Hwang T.L., Hung Y.C., Chang H.W.: "Adenoid cystic carcinoma of Bartholin's gland". *Taiwan. J. Obstet. Gynecol.*, 2012, 51, 119.
- [5] Takatori E., Shoji T., Miura J., Takeuchi S., Sugiyama T.: "Chemoradiotherapy with irinotecan (CPT-11) for adenoid cystic carcinoma of Bartholin's gland: A case report and review of the literature". *Gynecol. Oncol. Case Rep.*, 2013, 4, 16.
- [6] Ramanah R., Allam-Ndoul E., Baeza C., Riethmuller D.: "Brain and lung metastasis of Bartholin's gland adenoid cystic carcinoma: a case report". *J. Med. Case Rep.*, 2013, 7, 208.
- [7] Kozakiewicz B., Dmoch-Gajzlerska E., Roszkowska-Purska K.: "Carcinomas and sarcomas of Bartholin gland. A report of nine cases and review of the literature". *Eur. J. Gynaecol. Oncol.*, 2014, 35, 243.
- [8] Hsu S.T., Wang R.C., Lu C.H., Ke Y.M., Chen Y.T., Chou M.M., et al.: "Report of two cases of adenoid cystic carcinoma of Bartholin's gland and review of literature". *Taiwan. J. Obstet. Gynecol.*, 2013, 52, 113.
- [9] Agolli L., Osti M.F., Armosini V., De Sanctis V., Valeriani M., Enrici R.M.: "Adenoid cystic carcinoma of Bartholin's gland receiving adjuvant radiation therapy: case report". *Eur. J. Gynaecol. Oncol.*, 2013, 34, 487.
- [10] Copeland L.J., Sneige N., Gershenson D.M., McGuffee V.B., Abdul-Karim F., Rutledge F.N.: "Bartholin gland carcinoma". *Obstet. Gynecol.*, 1986, 67, 794.
- [11] Anderson R.J., Johnston W.W., Szpak C.A.: "Fine needle aspiration of adenoid cystic carcinoma metastatic to the lung. Cytologic features and differential diagnosis". *Acta Cytol.*, 1985, 29, 527.
- [12] Lelle R.J., Davis K.P., Roberts J.A.: "Adenoid cystic carcinoma of the Bartholin's gland: the University of Michigan experience". *Int. J. Gynecol. Cancer*, 1994, 4, 145.
- [13] Yang S.Y., Lee J.W., Kim W.S., Jung K.L., Lee S.J., Lee J.H., et al.: "Adenoid cystic carcinoma of the Bartholin's gland: report of two cases and review of the literature". *Gynecol. Oncol.*, 2006, 100, 422.
- [14] Dodson M.G., O'Leary J.A., Orfei E.: "Adenoid cystic carcinoma of the vulva. Malignant cylindroma". *Obstet. Gynecol.*, 1978, 51, 26s.
- [15] Wahlstrom T., Vesterinen E., Saksela E.: "Primary carcinoma of Bartholin's glands: a morphological and clinical study of six cases including a transitional cell carcinoma". *Gynecol. Oncol.*, 1978, 6, 354.
- [16] Vandeginste S., Geerinckx K., Vanneste G.: "Adenoid cystic carcinoma of Bartholin's gland: two cases". *J. Obstet. Gynecol.*, 1999, 19, 559.
- [17] Lopez-Varela E., Oliva E., McIntyre J.F., Fuller A.F. Jr.: "Primary treatment of Bartholin's gland carcinoma with radiation and chemoradiation: a report on ten consecutive cases". *Int. J. Gynecol. Cancer*, 2007, 17, 661.

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