

case report

Case report from Mayo Clinic: Locally advanced Bartholin gland carcinoma

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Tumors of the Bartholin gland are rare, comprising less than 5% of all vulvar malignancies. Treatment is largely based on that of vulvar and anal squamous cell carcinomas. A case of invasive, grade 4, poorly differentiated squamous cell carcinoma of the Bartholin gland is presented. Our patient, a 47-year-old woman, had a history significant for cervical intraepithelial neoplasia treated with conization, type 2 diabetes mellitus, and tobacco use. The course of treatment included preoperative radiotherapy plus 5-fluorouracil and cisplatin chemotherapy, followed by restaging and posterior exenteration in combination with vaginal reconstruction.

Key words: vulvar neoplasms – radiotherapy – drug therapy – surgery – Bartholin gland

Introduction

Accounting for less than 5% of all vulvar malignancies, primary carcinoma of the Bartholin gland is rare. Cancers arising in the Bartholin duct are most commonly adenocarcinomas or squamous cell carcinomas; occasionally transitional cell, adenosquamous, and adenoid cystic carcinomas may develop. A case of locally advanced Bartholin gland carcinoma was seen recently at Mayo Clinic.

Received 6 June 2007
Accepted 23 June 2007

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Case Report

A 47-year-old woman first noted a lump in the region of the introitus and labia majora in February 2006 and was evaluated by her local gynecologist. Her only symptom, other than mass effect, was minor constipation.

On examination under anesthesia, the patient was found to have a 5- to 7-cm by 7-cm mass that was believed clinically to arise from the region of the left-sided Bartholin duct. It was located anterior to the rectum and posterior and lateral to the vagina and extended to the region of the rectal sphincter. There was no involvement of the vulva, vaginal mucosa, or cervix on physical examination. A 2-cm mass was palpable in the left groin.

The patient underwent an extensive multimodality and multispecialty evaluation. Magnetic resonance imaging showed

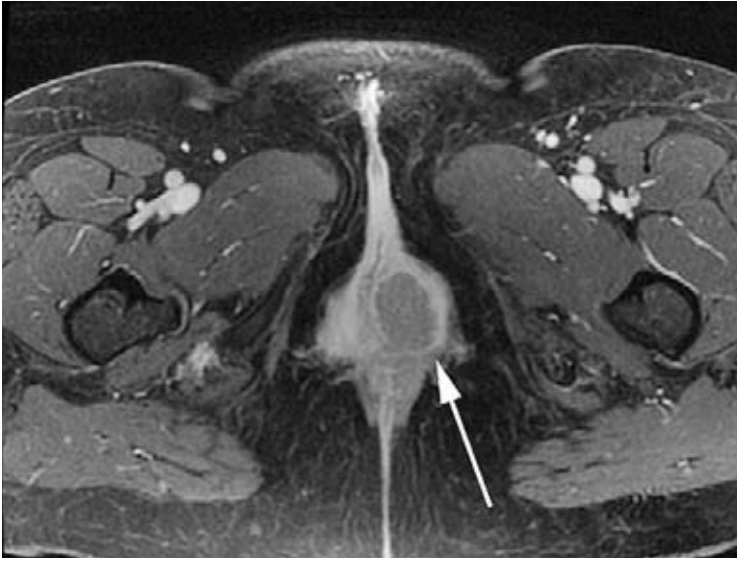


Figure 1. Axial T1-weighted magnetic resonance imaging before radiotherapy shows the primary Bartholin tumor (arrow).

a 5.1×3.8×4.5-cm lobulated enhancing mass arising between the vagina and rectum which appeared to encase the anterior and left lateral walls of the rectum (Figure 1). Perirectal lymph nodes of up to 1.6 cm were noted, as was a 2.0×1.5-cm enhancing lymph node in the left inguinal region, consistent with metastatic disease. Computed tomography (CT), chest radiography, and positron emission tomography (PET)/CT indi-

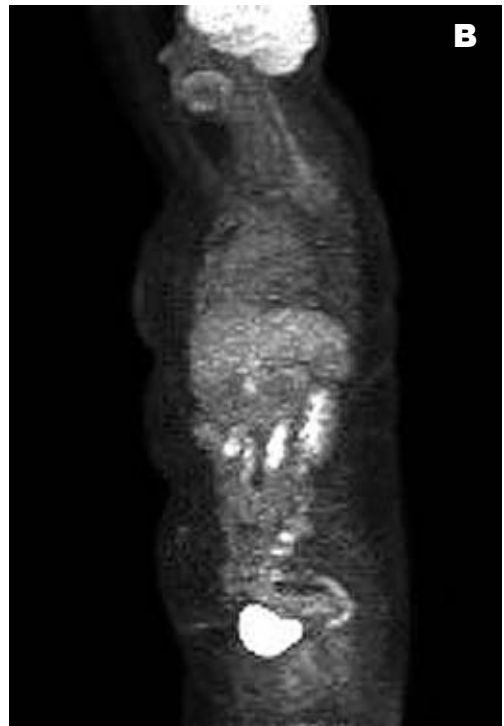
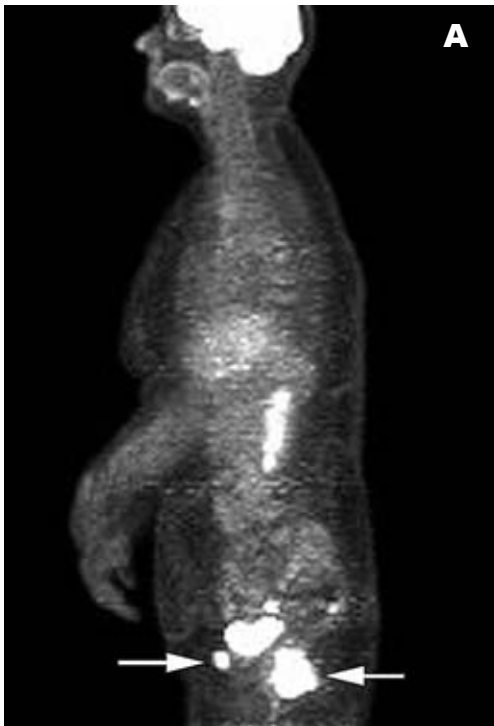


Figure 2. Lateral ¹⁸fluorodeoxyglucose (FDG)-positron emission tomography. A, Image before treatment. Arrows show location of the left inguinal nodal metastases superiorly and primary tumor inferiorly. B, Image 1 month after radiotherapy and chemotherapy showing a complete response by FDG signal.

Table 1. Intensity-Modulated Radiotherapy Prescription

Tumor dose	Description	Normal tissue constraints
PTV 51.25 Gy in 2.05-Gy fractions	Gross tumor volume (including primary tumor, gross perirectal adenopathy, and gross inguinal adenopathy) + 13- to 15-mm margin	Bladder V _{51.25Gy} <2% V _{40Gy} <30%
PTV 45.00 Gy in 1.80-Gy fractions	Radiographically uninvolved pelvis (excluding bladder and small bowel) and presacrum below the level of the bifurcation of the iliac vessels, and bilateral inguinal and external iliac lymph nodes	Small bowel V _{51.25Gy} <2% V _{45Gy} <15% V _{30Gy} <20%
PTV 42.50 Gy in 1.70-Gy fractions	Common iliacs and presacrum to the mid L5 level	Perineum V _{52Gy} <2% V _{20Gy} <20% Femoral heads V _{45Gy} <2% V _{35Gy} <20% Uterus (used as an avoidance structure to conform dose to pelvis and nodal structures) V _{51.25Gy} <2% V _{40Gy} <30%

PTV, planning target volume; V, volume.

cated no evidence of distant metastases (Figure 2 A). Endoscopic ultrasonography showed numerous abnormal perirectal nodes that were round and echopoor and measured from a few millimeters to 1.2 cm in diameter. The tumor involved the anterior portion of the anal sphincter mechanism.

Transrectal biopsy of the primary tumor in February 2006 indicated invasive, grade 4 (of 4), poorly differentiated squamous cell carcinoma. The neoplastic cells were strongly reactive for CK7 and showed normal staining for MLH1, MSH2, MSH6, and PMS2. The tumor lacked staining for CK20, CDX2, and estrogen receptor.

The patient's medical history was significant for cervical intraepithelial neoplasia treated with cervical conization in 1981.

Additionally, the patient had a history of tobacco use and type 2 diabetes mellitus controlled with oral medications. She had never received radiotherapy or chemotherapy.

The departments of radiation oncology, medical oncology, gynecologic surgery, and gastroenterology were consulted regarding treatment; it was believed that the optimal course of treatment would involve preoperative radiotherapy and 5-fluorouracil (5-FU) and cisplatin chemotherapy, followed by restaging and posterior exenteration in combination with vaginal reconstruction.

In March 2006, the patient began concurrent chemotherapy and intensity-modulated radiotherapy (IMRT) to a total dose of 51.25 Gy in 25 fractions to regions of gross

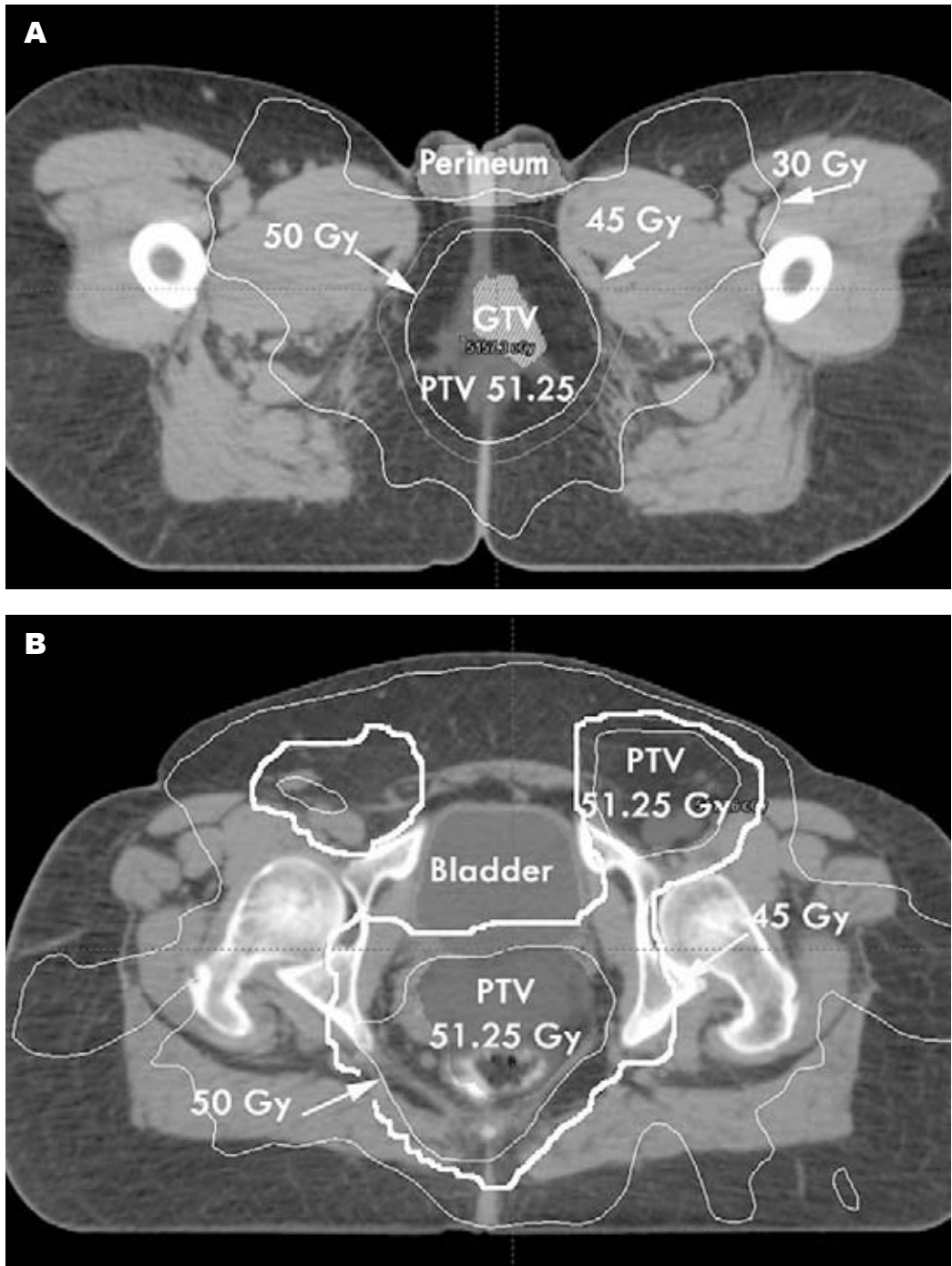


Figure 3. Intensity-modulated radiotherapy isodose curves showing relative sparing of the perineum (A) and sparing of the bladder and central pelvis (B). (Planning target volume [PTV] 45.00 Gy and femur volumes deleted for clarity of illustration.) GTV, gross tumor volume.

tumor, with margins involving the Bartholin gland region and the perirectal and left inguinal adenopathy. IMRT was delivered with 6-MV photons after a CT simulation of the patient in a supine, frog-legged position with a full bladder. Full technical details of the IMRT prescription are shown in Table 1. All 3 planning target volume (PTV) dose levels were treated simultaneously (Figure 3). The patient received 2 cycles of cisplatin and 5-FU chemotherapy intravenously over 4 days in weeks 1 and 4 of radiotherapy. Cisplatin was given at 75 mg/m² on day 1 of each chemotherapy cycle, and 5-FU, by ambulatory continuous venous infusion over days 1 through 4 at 225 mg/m² per day. The patient had radiation toxicity (by the Common Terminology Criteria for Adverse Events v3.0) consisting of grade 3 dermatitis, grade 2 leukopenia, grade 2 dysuria and frequency, and grade 3 enteritis and proctitis.

She was able to complete the prescribed course of radiotherapy and chemotherapy within 32 days total time, despite the acute toxicity. The patient returned for re-evaluation approximately 4 weeks after completion of radiotherapy and chemotherapy, at which time the acute toxicity had resolved. Physical examination showed complete resolution of the primary tumor, and pelvic examination showed no evidence of abnormalities. A PET/CT study indicated no ¹⁸fluorodeoxyglucose uptake at the site of the primary tumor and lymph nodes, no evidence of the left inguinal adenopathy, and near resolution of the primary tumor and perirectal lymphadenopathy by PET tracer uptake (Figure 2 B).

The patient then underwent posterior enteration and vaginal reconstruction with a vertical rectus abdominis muscle flap. Pathologic review of the resected specimen showed no residual tumor. An ill-defined submucosal mass was seen in the region of the anterior rectal wall showing fibrosis and

histiocytic inflammation but no evidence of tumor. Nine lymph nodes were negative for tumor. The groin was not dissected at the time of surgery.

The patient returned for re-evaluation 5 months after surgery. Her postoperative course had been unremarkable. She reported no pain or gastrointestinal tract, skin, or genitourinary symptoms. Physical examination showed no evidence of recurrent tumor, in either the groin or the pelvis. No lower extremity edema was present. CT performed 1 month after surgery showed no evidence of pathologic processes other than postoperative changes associated with the resection and muscle flap. She will undergo re-examination in our clinic approximately every 12 weeks for 2 years, then every 6 months for 3 years, and yearly thereafter.

Discussion

The incidence of Bartholin gland tumors is highest among women in their 60s, with the median age of diagnosis being 57 years. Most patients with a Bartholin gland malignancy do not have a history of other Bartholin gland disorders. Bartholin gland enlargement in a postmenopausal woman should raise suspicions of malignancy because benign inflammatory disease typically does not occur in this age group. A biopsy should be performed for any abnormal growth of the Bartholin gland if the patient is older than 40 years.

The differential diagnosis for a Bartholin gland tumor most commonly includes cysts and abscesses, which occur in 2% of women, and other vulvovaginal disorders, such as vulvar carcinoma, acrochordons, hidradenomas, other dermatoses, and condyloma acuminata. The Bartholin gland is composed of columnar epithelium, and the ducts are lined by stratified squamous epithelium, which changes to transitional

cell epithelium toward the terminal ducts. Squamous cell carcinoma is the only lesion of the Bartholin gland linked to human papillomavirus. Metastases are common as a result of the copious supply of vascular and lymphatic networks in the area. The most common presentation of a Bartholin gland carcinoma is a painless vulvar mass.^{1,2}

Few data are available on the associated treatment of Bartholin gland carcinoma; such treatment is largely based on that of vulvar and anal squamous cell carcinomas. No large randomized controlled trials have been published on the treatment of advanced vulvar cancer. Moore *et al.*³ reported a phase II study by the Gynecologic Oncology Group examining the use of preoperative chemoradiotherapy to avert the need for more radical surgery. In this study, 73 evaluable patients with clinical stage III-IV squamous cell vulvar carcinoma were treated with a planned split course: twice-daily concurrent cisplatin (50 mg/m²) and 5-FU (1,000 mg/m²) on days 1 through 4 and radiotherapy (to 47.6 Gy), followed by surgical excision of the residual primary tumor plus bilateral inguinofemoral lymph node dissection. A total of 33 patients had no visible vulvar cancer after combined chemoradiotherapy.³ The authors concluded that preoperative chemoradiotherapy in advanced squamous cell carcinoma of the vulva is feasible and may decrease the need for more radical surgery.³ In another study, Han *et al.*⁴ concluded that concurrent chemoradiotherapy as primary treatment for locally advanced vulvar cancer decreases local relapse rate and improves disease-specific and overall survival versus radiotherapy alone.

Unlike vulvar cancers, treatment of anal cancer has been evaluated in several randomized controlled trials. At one time, abdominoperineal resection was considered the treatment of choice for anal cancer.⁵ However, the standard of care has since be-

come infusion chemotherapy with 5-FU and mitomycin C (MMC) along with radiotherapy (45-50 Gy). Surgery is now reserved as a last resort.⁵ A phase III randomized controlled trial assigned 110 patients to either definitive radiotherapy alone or radiotherapy combined with 5-FU/MMC.⁶ The patients received 45 Gy given in 5 weeks, followed by a 6-week rest period and then a 15- to 20-Gy boost to a total dose of 60 to 65 Gy. The chemotherapy regimen consisted of 750 mg/m² of 5-FU on days 1 through 5 and 29 through 33 and a single dose of MMC (15 mg/m²) on day 1. Concurrent 5-FU/MMC with radiotherapy significantly improved the locoregional control rate and significantly decreased the need for colostomy.⁶

A study by the UK Co-ordinating Committee on Cancer Research had a similar design; 585 patients were randomly assigned to 45 Gy over 4 to 5 weeks alone or combined with chemotherapy (5-FU [1,000 mg/m² for 4 days or 750 mg/m² for 5 days by continuous infusion] during the first and final weeks of therapy and MMC [12 mg/m²] on day 1).⁷ The combined chemotherapy and radiotherapy arm had a significant increase in local control rate. The authors concluded that standard treatment for anal cancer should be a combination of radiotherapy and infusion of 5-FU and MMC.⁷ A phase III randomized trial reported by Flam *et al.*⁸ aimed to determine the importance of MMC in the combined treatment of anal cancer. The study showed significantly increased colostomy-free survival, disease-free survival, and local control rates. The authors concluded that despite greater toxicity, the use of MMC is justified.⁸

Our patient was treated with combined-modality therapy similar to that used for patients in the study of squamous cell vulvar carcinoma by Moore *et al.*³ One notable difference, however, was our use of IMRT. IMRT of the pelvis has been shown by numerous investigators to be safe, feasible,

and effective in terms of acute and chronic toxicities, as well as clinical outcomes.⁸⁻¹² Specifically, Garofalo *et al.*¹³ evaluated IMRT planning in patients with vulvar cancer undergoing treatment to both the pelvic and inguinal fields. As compared with conventional techniques, IMRT was associated with a decreased volume of small bowel, bladder, rectum, and femoral heads receiving the prescription dose. Recently, investigators from the University of Chicago and Mayo Clinic Rochester have published their experience with IMRT and anal cancer, which showed favorable toxicity and clinical outcomes.¹⁴⁻¹⁵

With successful completion of aggressive combined-modality therapy using concurrent chemotherapy and radiotherapy, a surgically verified complete pathologic response was obtained in the patient presented here. However, metastases of the abdomen and liver eventually developed. At this time, decisions regarding salvage chemotherapy and other potential palliative measures are being considered for this patient.

Acknowledgment

Editing, proofreading, and reference verification were provided by the Section of Scientific Publications, Mayo Clinic.

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