Kaohsiung Journal of Medical Sciences (2011) 27, 150–154

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CASE REPORT

Locally advanced female urethral adenocarcinoma of enteric origin: The role of adjuvant chemoradiation and brief review

胚胎起源自腸道之局部性晚期女性尿道腺癌：輔助性化學及放射線治療的角色及文獻回顧

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Received 18 January 2010; accepted 2 September 2010
Available online 16 February 2011

KEYWORDS
Adjuvant chemotherapy;
Chemoradiation;
Irinotecan;
Urethral adenocarcinoma;
Urethral carcinoma

關鍵詞
輔助性化學治療;
化學及放射線治療;
喜樹鹼;
尿道腺癌;
尿道腫瘤

Abstract Primary female urethral adenocarcinoma (FUA) is rare and has a poor prognosis. The common manifestations include urethrorrhagia, urinary frequency, dysuria, urethral obstructions, focal tenderness, and urinary tract infection. These symptoms are neither diagnostic nor pathognomonic; therefore, a delay in diagnosis and even a misdiagnosis is hardly uncommon. The histogenesis of FUAs may have derived from urethritis glandularis, Mullerian ducts, Skene's glands, or mixed origins. Tumors of different embryologic origins displayed heterogeneous pathological morphology and immunohistochemistical phenotypes. Because of its rarity and the lack of large-scale studies, there is no current consensus on the optimal treatment of urethral adenocarcinomas. Here, we report two cases of locally advanced FUA of enteric origin. They manifested as slightest warning symptoms of urinary tract infection and stress urinary incontinence, respectively. One patient died of disease progression 2 months after curative operation. The other patient underwent surgery followed by adjuvant irinotecan-containing chemoradiation, and the effect was at least modest. Hence, we recommend adjuvant chemoradiation in locally advanced FUA. Individualizing cancer care of chemoregimens in accordance with the tumor origins may probably be beneficial in FUAs.

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doi:10.1016/j.kjms.2010.12.009

摘要 原發性女性尿道腺癌為一罕見且預後不佳的惡性腫瘤。常見臨床表徵包含出血、頻尿、尿道阻塞症狀、局部疼痛或泌尿道感染。臨床因無特異表現，延誤診斷或誤診並非罕見。過去文獻證實原發性女性尿道腺癌病理型態具多樣性，因腫瘤起源自不同組織，而有不同細胞型態及免疫組織化學染色特徵。此外，原發性女性尿道腺癌屬罕見疾病且缺乏大型臨床試驗，目前對最佳治療方式缺乏共識。在此報告兩例女性尿道腺癌個案，病患均屬於局部性晚期病灶且起源自腸道，兩人分別以泌尿道感染及應力性失禁為初始表現。其中一人接受治癒性手術後2個月死於疾病進展，另一個病人則於術後接受輔助性放射線治療及含有喜樹鹼（irinotecan）的輔助性化學治療，其成效不俗。因而針對局部性晚期原發性女性尿道腺癌，建議病患術後接受輔助性化學及放射線治療，同時，依據腫瘤胚胎起源選擇個別不同的化療處方或許是未來可考量的方向。

Introduction

Primary female urethral adenocarcinoma (FUA) is rare. Ten percent to 16% of female urethral carcinomas are adenocarcinomas, and they comprise less than 0.003% of all female urogenital tract malignancies [1,2]. The common symptoms of FUA consist of urethrorrhagia, urinary frequency, dysuria, urethral obstruction, focal tenderness, and urinary tract infection [3]. However, neither of these symptoms are diagnostic nor pathognomonic; hence, delayed diagnosis or misdiagnosis is not uncommon.

During October 1980 to December 2009, there were 35 patients with pathologically proven urethral adenocarcinoma in our hospital. Only two patients had true primary FUA. Because of its rarity and the lack of large-scale studies, there is no current consensus on the optimal treatment. We retrospectively compared the clinical manifestations, pathological characteristics, treatment modalities, and outcomes in these two patients with locally advanced disease. To our knowledge, adjuvant irinotecan-containing regimen in urethral adenocarcinoma was never reported before.

Case presentation

Case 1

A 69-year-old woman presented with urinary frequency for 1 month. She was treated as urinary tract infection in a local hospital and her symptoms subsided for a short period. In September 2002, she visited our hospital after symptoms relapsed, and a noticeable mass was found in the anterior vaginal wall during Foley catheterization. A gynecologist was consulted, but no gynecological abnormality was noted in ultrasonography. The abdominal computed tomography (CT) showed urethral diverticulum with stone, and magnetic resonance imaging (MRI) revealed a suspicious periurethral tumor with irregular border and intratumoral hemorrhage. Chest X-ray and whole body bone scan were negative. So she received radical cystectomy with ileal conduit diversion. The pathology revealed moderately to poorly differentiated adenocarcinoma arising from the urethral diverticulum (Fig. 1A). Tumor cells invaded the submucosa of the vaginal wall with vascular involvement (pT3N0M0). Immunohistochemically, the tumor cells were

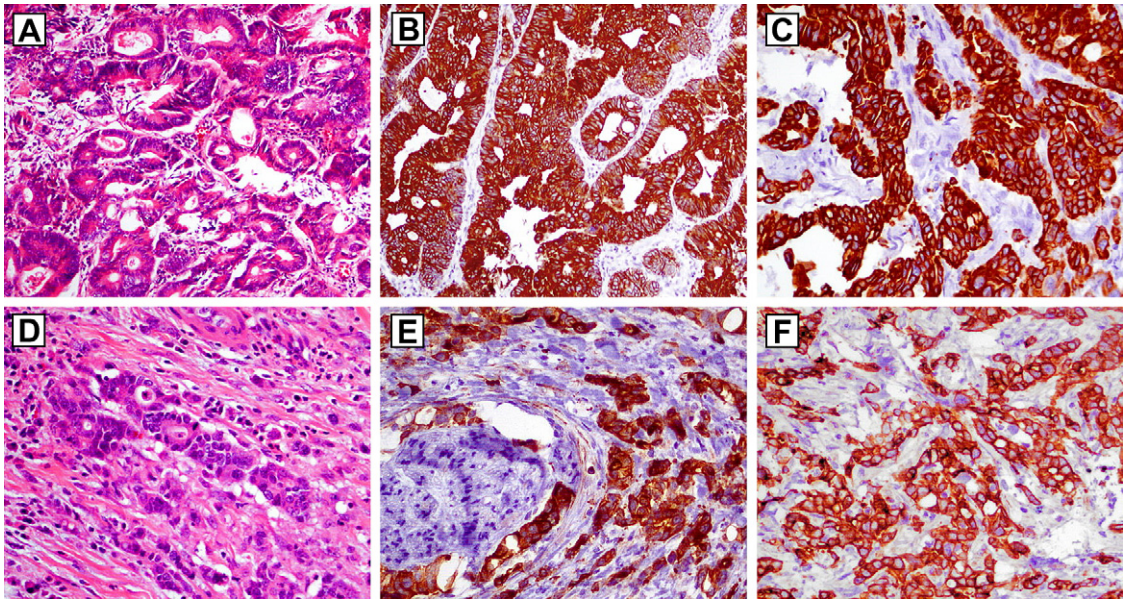

Figure 1. (A—C) In Case 1, the tumor was moderately to poorly differentiated adenocarcinoma with positive CK7 and CK20 immunostains. (D—F) In Case 2, the neoplasm was moderately differentiated adenocarcinoma, which was composed of clusters of neoplastic cells in a glandular pattern. Immunohistochemically, these tumor cells were positive for CK7 and CK20 stains (400×; hematoxylin and eosin in A and D; CK7 in B and E; CK20 in C and F). CK = cytokeratin.

positive for cytokeratin 7 (CK7) and cytokeratin 20 (CK20) and negative for prostatic-specific antigen (PSA) immunostains (Fig. 1B and C). The patient asked to postpone adjuvant chemoradiation because of persistent epigastragia. Panendoscopy disclosed esophageal and gastric ulcer only. However, she complained about shortness of breath 2 months after operation, and chest X-ray revealed multiple metastases in the lung. Chest CT reconfirmed the metastases. Her family requested do-not-resuscitate and she died of respiratory failure soon.

Case 2

For stress urinary incontinence, a 49-year-old woman received bladder neck suspension with tension-free vaginal tape in a local hospital. Since the completion of the above procedure, she began to complain about urinary frequency and dysuria, and the symptoms were considered to be associated with oversuspension. She received two further operations aiming to release the tension. However, her symptoms persisted and she attended our clinic 6 months after tension-free vaginal tape in April 2008. Cystometrogram and cystoscopy were aborted because of urethral stricture. One urethral-vaginal fistula was noted when she underwent urethroplasty, and pathology of the biopsy turned out to be adenocarcinoma. The abdominal CT revealed a hypodense nodule at the urethra with posteriolateral extension to the vagina. The pelvic MRI showed a urethral tumor, 3.5 cm in size, with anterior vaginal wall invasion. No other tumor was demonstrated. All of her serum tumor markers were within normal range, including PSA. Bone scintigraphy had no evidence of bony involvement. She received urethrectomy, anterior exenteration, ileal conduit, and pelvic lymph nodes dissection. Pathology demonstrated moderately differentiated adenocarcinoma (Fig. 1D) with invasion of the periurethral, vagina, paravaginal, paracervix, and prerectal soft tissue (pT4N0M0). Surgical margins could not be properly evaluated. Immunohistochemically, these tumor cells were positive for CK7 and CK20 immunostains and negative for PSA staining (Fig. 1E and F). For this unclear margin-free advanced stage and no consensus on the treatment, we commenced her on adjuvant radiotherapy followed by six cycles of chemotherapy with Douillard regimen containing irinotecan, fluorouracil, and leucovorin, one of the best-known combinations in colorectal cancer. After finishing two cycles of chemotherapy, she was intolerant to asthenia. No evidence of tumor recurrence was found in the following CT and during gynecologist consultation, thus she asked to discontinue the chemotherapy. Six months after the operation, she suffered from painful induration in the suprapubic area. Pathology confirmed the presence of metastases after incisional biopsy followed by wide excision. She was reluctant to undergo salvage chemotherapy and received radiotherapy only. Another 7 months later, her abdominal CT, MRI, and bone scan documented a tumor relapse in the pubic symphysis, but she refused palliative chemotherapy. She suffered from fever and low abdominal pain a month later. Abdominal CT disclosed bowel obstruction related to adhesion band. Another cystic lesion with gas trapping and soft tissue swelling was noted at the midline rectus muscle, and abscess formation was likely. The abscess was spontaneously drained from the previous incision line, followed by wound dressing, debridement, and final suture. Nevertheless, stool-like materials leaked from the suture and her symptoms subsided after the fistula formation. She was under hospice care since then.

Discussion

Urinary tract infection and stress urinary incontinence are two of the most common conditions among women who seek medical help [4,5]. Less than 10% of female urethral cancer patients initially present with urinary incontinence and only 5% with urinary tract infection [3,6]. Because these symptoms are nonspecific, we should take into account the possibility of urethral carcinomas in general practice to make an early diagnosis and to prevent unnecessary interventions and severe complications (obstruction, stricture, and fistula formation).

In addition, FUA may arise from urethritis glandularis, Mullerian ducts (paramesonephric ducts), Skene's glands (paraurethral glands), or mixed origins. The major histological subtype is columnar/mucinous adenocarcinoma and most columnar/mucinous lesions originate from urethritis glandularis that transformed from intestinal metaplasia. The microscopic appearance resembles colonic or endometrial adenocarcinoma and is immunohistochemically positive for CK7, CK20, and mAbDAS1 stains [7,8]. The morphological pattern of either the signet ring cell or the columnar/mucinous form depends on the degree of neuroendocrine differentiation and mucin production. Some FUA with proximal paraurethral duct origin come

Table 1 Histogenesis and pathological phenotypes of morphology and immunohistochemistry

Histogenesis	Embryologic origin	Typical morphology	Positive immunostains
Urethritis glandularis	Intestinal metaplasia	Columnar/mucinous	CK7, CK20, mAbDas1[a]
Mullerian duct[b]	Ovarian or fallopian tube	Clear cell	CA125
Paraurethral duct			
Proximal part	Cystic glandular metaplasia	Signet ring cell[c]	CEA
Distal part	Skene's gland	Cribriform	PSA, PAP

[a] mAbDas1 is a monoclonal antibody reactive in areas of intestinal metaplasia.
[b] Mullerian duct or paramesonephric duct.
[c] Neuroendocrine differentiation correlates with mucin production.
CEA = carcinoembryonic antigen; CK = cytokeratin; PAP = prostatic acid phosphatase; PSA = prostatic-specific antigen.

Table 2 Adjuvant chemoradiation in locally advanced female urethral adenocarcinomas

Author	Stage	Adjuvant tx	Chemotherapy regimens	DFS	Results
Awakura et al. [12]	T3N0M0	C/T,[a] R/T	Cisplatin, 5-fluorouracil	NED	NED for 2 yr
Davis et al. [13]	T4N0M0	CCRT,[b] C/T	Carboplatin, paclitaxel	NED	DOC
Dimarco et al. [14]	T4N1M0	R/T, C/T	Cisplatin-based	3 mo	DOD at 5 mo
Dimarco et al. [14]	T4N0M0	CCRT	Cisplatin-based	13 mo	DOC at 23 mo
Tanaka et al. [15]	T4N0M0	CCRT	Cisplatin, TS-1	5 mo	DOD at 14 mo
Koizumi et al. [16]	TxN1M0	R/T, C/T	Cisplatin, 5-fluorouracil	6 mo	DOD at 20 mo
Case 2	T4N0M0	R/T, C/T	5-Fluorouracil, irinotecan	6 mo	Survival > 2 yr

[a] Intra-arterial chemotherapy followed by intravenous chemotherapy.
[b] Neoadjuvant CCRT.
CCRT = concurrent chemoradiation; C/T = chemotherapy; DFS = disease-free survival; DOC = death from other causes; DOD = death from disease; mo = months; NED = no evidence of disease; R/T = radiation; tx = treatment.

from cystic glandularis with positive carcinoembryonic antigen staining [9]. Behind columnar/mucinous type adenocarcinoma, there are around 15% of clear cell adenocarcinomas in FUA [10]. The hypothesis of clear cell adenocarcinomas arising from the Mullerian duct (origin of ovary and fallopian tube) is supported by positive carbohydrate antigen 125 immunostains [1]. Finally, the minor subtype is cribriform adenocarcinoma. Tumors with distal paraurethral duct origin come from female Skene's glands (homogeneity of male prostate gland) driving from the same cribriform morphology are matched by positive immunostains of PSA and prostatic acid phosphatase [11]. Meanwhile, elevated serum PSA that declines rapidly after operation provides further evidence (Table 1).

Given the rarity and lack of large-scale studies, the recommendations in the treatment of FUA are based on general principles and extrapolations from other diseases. Treatment choices for tumor of less than 2 cm include irradiation or curative surgery with/without adjuvant radiation. For bulky lesions, brachytherapy or external beam radiotherapy significantly improves the local control rate and preserves organ functions [6]. For locally advanced disease, multimodality therapy is the current trend [12—17]. Preoperative or postoperative irradiation is recommended, but the role of chemotherapy in reduction of local recurrence or distant metastasis is not well documented. The platinum-based chemotherapy is usually given based on the pooling data of metastatic nontransitional cell carcinomas of the urothelial tract [18]. However, the limitation in applying the result was the small percentage of FUA patients in the retrospective study. Rather, embryologic origin was never correlated with the treatment modalities and outcomes. Another study reported that the prognosis of advanced urethral carcinoma has been improved by chemoradiation chiefly with 5-fluorouracil and mitomycin-C [17]. The case series of locally advanced FUA undergoing adjuvant chemoradiation found in the literature were summarized in Table 2. According to the limited data, either local or distant recurrence mostly occurred within the first 6 months even after aggressive adjuvant therapy (median duration, 5.5 months; range, 3—13 months). Patients receiving adjuvant concurrent chemoradiation had similar outcome with those taking alternative treatment (Table 2). In addition to histology, the tumor size is the only independent prognostic factor of female urethral cancer in a multivariate analysis [6].

In our patients, the microscopic morphology of tumors was both columnar glandular patterns with strong positive for CK7, CK20 and negative for PSA immunostains. Therefore, the diagnosis of locally advanced FUA of enteric origin was preferred. In Case 1, the patient died of rapid disease progress 2 months after curative operation. In Case 2, the patient received adjuvant radiation followed by Douillard regimen, which was a well-documented first-line chemotherapy in metastatic colorectal cancer [19]. Despite the incomplete courses of chemotherapy, this patient had a disease-free survival period of 6 months and the effect was at least modest compared with the median disease-free duration, 5.5 months, in the previous review. However, it was inconclusive whether radiation or chemotherapy or both approaches contributed to the outcome. Furthermore, the treatment for our patient was discontinued because of intolerance of the side effect, and therefore we were unable to predict the superior outcome after full courses of chemotherapy. However, the indirect evidence supporting the use of Douillard regimen in FUA comes from urachal carcinomas (enteric type adenocarcinomas of urinary bladder). The efficacy of 5-fluorouracil-based chemotherapy is supported in the currently accruing clinical trials [20].

We conclude that adjuvant chemoradiation plays a role in locally advanced FUA. In addition, irinotecan-containing regimen proved at least modest efficacy in advanced FUAs of enteric origin. Moreover, individualizing cancer care of chemoregimens in accordance with the tumor embryologic origins seems reasonable. However, the feasibility should be further confirmed by larger prospective trials.

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