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Case Report

Primary small cell carcinoma of vagina: report of two cases

Jingni Zhang[1], Yi Luo[1], Rui Yuan[1,*]

[1] *Department of Obstetrics and Gynecology, the First Affiliated Hospital of Chongqing Medical University, 400016 Chongqing, China*

*Correspondence: Yrui96@hospital.cqmu.edu.cn (Rui Yuan)

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Background: Primary small cell carcinoma of vagina (SCCV) is highly malignant and rare. Only 39 patients with this malignancy can be found in a search of the PubMed and MEDLINE database, and most of them died within 12 months of diagnosis. *Cases*: We report two patients with primary vaginal small cell carcinomas. Their tumors show similar histologic and ultrastructural neuroepithelial elements. Both of them underwent radical surgery, received different adjuvant therapy, and had different outcomes. One is without recurrence 36 months after surgery and the other recurred within 2 months of completing treatment. *Conclusion*: Although surgery for the treatment of early-stage disease is suggested, surgery followed by chemotherapy and radiation may be superior to surgery alone. Receiving chemotherapy and radiotherapy as soon as possible after surgery may improve patient prognosis.

Keywords

Small cell carcinoma; Immunohistochemical staining; Chemo-radiotherapy; Survival time

1. Introduction

Over 95% of primary small cell carcinomas (SCC) occur in the lungs, and a small number of primary SCC originate in the genital tract. SCC accounts for only 1%–2% of all gynecological malignant tumors [1]. It occurs most frequently in cervix and rarely in the vagina. Most of the patients die within 1 year of diagnosis [1]. After searching the PubMed and MEDLINE database, we found only 39 reported cases [2–30] of primary vaginal small cell carcinoma (SCCV) and the current managements have usually resulted in poor outcomes, however, due to the rarity of the lesion, there is no standard guideline of treatment.

2. Case 1

A 51-year-old woman complaining of vaginal discharge was admitted to the hospital in December 2017. She had no significant medical history. Thin-prep cytology test of cervix was benign and HPV DNA assaywas negative. The special tumor marker of SCC, neuron specific enolase (NSE), and other tumor markers such as squamous cell carcinoma antigen were almost normal. The physical examination showed a neoplasm about 2 cm in the posterior fornix of vagina. Hematoxylin-eosin (HE) staining of biopsy tissue was consistent with malignancy (Fig. 1). The immunohistochemical stains demonstrated positivity for chromogranin A (CgA) and synaptophysin (Syn) (Fig. 2). The MRI film of the pelvis showed that the lymph nodes were not enlarged. PET/CT scans were negative for metastatic diseases.

Subsequently she underwent radical hysterectomy with partial vaginectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Gross examination of the specimen found the greatest tumor width was 2 cm with invasion of deep soft tissue. Microscopy showed the tumor deeply infiltrated all layers of the vaginal wall but didn't extend beyond tunica adventitia to paravaginal tissue, and cancer thrombus was found in vessels. Lymph nodes and vaginal margins were negative. Immunohistochemical analysis was consistent with the earlier results. Finally, clinical stage I (T1N0M0) SCCV was confirmed. Postoperatively she received etopside a dose of 100 mg/m^2 and cisplatin at a dose of 60 mg/m^2 every 3 weeks for 6 courses, followed by external beam radiotherapy to the pelvis, 45 Gy in 25 fractions. Eight months after initial visits, her MRI of the pelvis demonstrated no evidence of local recurrence or distant metastases. She has remained clinically free of disease of 36 months since surgery.

3. Case 2

An asymptomatic 44-year-old woman was found to have a 2 $\times$ 2 cm, right-sided, firm vaginal polypoid mass in October 2019. She had no signifificant medical or surgical history. Neuron specific enolase (NSE) was normal. A biopsy was consistent with a small cell malignant neoplasm. A MRI of the pelvis confifirmed the presence of a vaginal mass arising from the right side of the vagina and a lymph node near the right side of upper vagina (Fig. 3). CT scan of lungs and Papanicolaou test were negative.

She received radical hysterectomy with partial vaginectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and paravaginal lymph node resection. Pathological examination showed tumor deeply infiltrating the vaginal wall with lymph nodes and vaginal margins negative. Immunohistochemical analysis showed positivity for CD56, CgA and Syn (Fig. 2). The disease was designated as clinical stage I (T1N0M0) SCCV. The patient was offered postoperatively concurrent chemoradiation. After receiving chemotherapy with etopside (100 mg/m^2) and nedaplatin (80 mg/m^2)

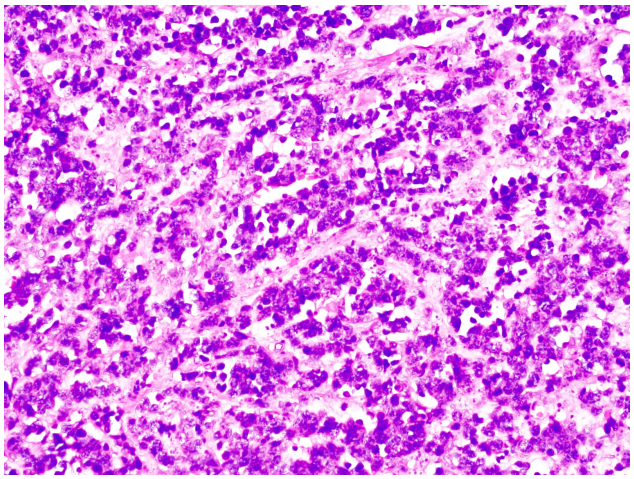

Fig. 1. Hematoxylin-eosin (HE) staining of biopsy tissue. It shows small cells crowding in sheets with deeply stained nucleic (Original magnification ×400).

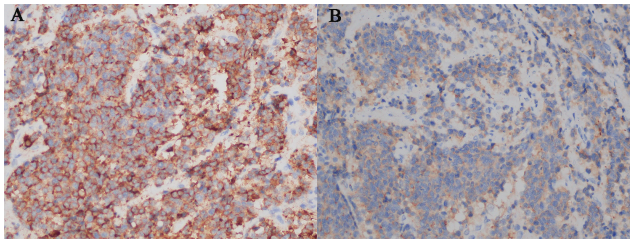

Fig. 2. Immunohistochemical stains under light microscope. It shows chromogranin A expression (A) and synaptophysin expression (B) (Original magnification ×400).

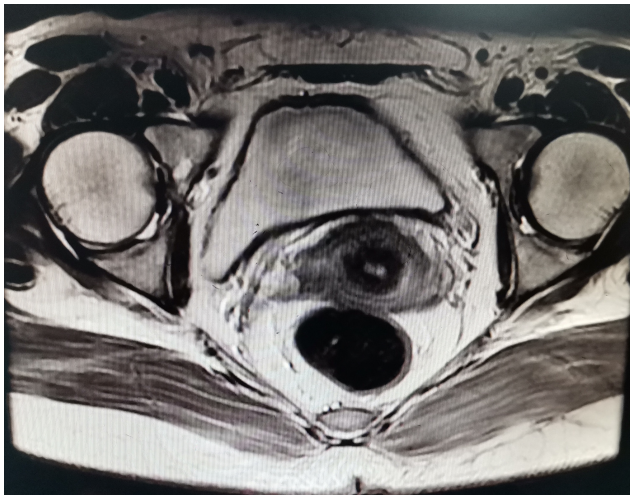

Fig. 3. A MRI film of the pelvis. The vaginal mass arising from the right side of the vagina shows slight high signal in T2WI.

for 4 courses, she declined further therapy. Two months later, PET/CT scans showed recurrence with local lesion and metastatic lesion in the liver. She underwent pelvic tumor cytoreductive surgery in July 2020, followed by chemotherapy with paclitaxel and nedaplatin. Her treatment was complicated by anemia resulting in death 14 months after her cancer diagnosis.

4. Discussion

The first case of SCCV was reported by Scully *et al.* [30] in 1984. SCCV is extremely aggressive and rarely reported with only 39 patients found in our search of the PubMed and MEDLINE database. SCCV may be asymptomatic with a lesion in vagina but usually manifest with postmenopausal bleeding or vaginal discharge. They may also manifest with symptoms due to metastasis, such as abdominal pain, and hemoptysis. Though it has been well known that SCC of cervix are associated with human papilloma virus (HPV) especially HPV 16 and18 infections, there is not definitive evidence to show that SCCV is related to HPV infection, because only one case [3] of SCCV reported HPV status.

The histologic appearance of SCC under light microscopy is small cells with round or oat-shaped nucleus, scant cytoplasm and deeply stained nucleoli to differentiate SCC form other tumors appearing as small blue cells such as lymphoma and sarcoma, immunohistochemical analysis is often performed. The positivity of neuroendocrine markers CD56, neuron-specific enolase (NSE), chromogranin A (CgA) and synaptophysin (Syn) are significant for diagnosis. As reported by Bing *et al.* [14], 7 cases were subjected to NSE and Syn, and all showed positivity. CgA was performed in 8 cases with 7 positive and 1 negative. The negativity of lymphocytotoxic antibody helps to exclude lymphoma. Thyroid transcription factor 1 (TTF-1) is a sensitive marker for SCC of pulmonary origin, but the expression in urinary bladder, uterine cervix and vagina has also been reported [14, 31], in other words, it is not specific enough to distinguish primary SCCV and SCC metastatic from the lung. Though the HE and immunohistochemical staining patterns of SCC in different parts of genital tract are similar [32], SCC metastatic from cervix or lung must be excluded before SCCV diagnosed. Thus clinical evaluation combined with radiographic examination and ThinPrep cytologic test (TCT) is necessary to determine whether there are cervical or pulmonary lesions.

Currently most studies about SCCV are case reports and there is no standard guideline for treatment. With the neuroendocrine phenotype, the management strategies for SCC of female genital tract are often adopted from strategies for SCC of the lung [32]. A clinical document about SCC of genital tract released by Society of Gynaecologic Oncology in 2011 suggested that the approach to managing SCC of the cervix could be extrapolated to SCCV. Radical excision was suggested in early-stage disease, and chemo-radiotherapy with platinum and etoposide is suitable for advanced cases [1]. Considering the different clinical outcomes of we reported two patients, we believe that supplementary radiotherapy and chemotherapy after surgery may be necessary for patients with early-stage disease. To date, 33 [2–5, 7–9, 11–15, 17–28] of the 39 patients with SCCV reported in the English literature are available for clinical and pathological

Table 1. Review of literatures about SCCV.

Literature	NO. Pa	Age, y	TNM stage	Primary therapy	Response	Outcome	Survival, mo
Present study	1	51	I: T1N0M0	Sequential: radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy; CT with EP; RT	CR	AWND	At least 36
	1	44	I: T1N0M0	Sequential: radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy; CT with EP	Recurrence with local and metastatic lesion	Died	14
Kombathula *et al.* in 2019 [2]	1	65	III: T2N1M0	Sequential: neoadjuvant CT; C-CR; adjuvant CT	CR	AWND	At least 22
Kostamo *et al.* in 2018 [4]	1	32	II: T2N0M0	Sequential: radical hysterectomy with partial vaginectomy, left oopexy, right salpingo-oophorectomy and right pelvic lymphadenectomy; CT with topotecan, paclitaxel, and bevacizumab; RT	CR	Died	34
Haykal *et al.* in 2018 [3]	1	56	I: T1N0M0	Sequential: CT with EP; C-CR with cisplatin/taxol	Ongoing treatment	Alive	At least 3
Yan WX *et al.* in 2016 [5]	1	43	IV: TXN1M1	C-CR with cisplatin and paclitaxel	CR	AWND	At least 21
Tamura *et al.* in 2013 [7]	1	81	I: T1NOMO	RT	CR	AWND	At least 20
Khurana *et al.* in 2013 [9]	1	37	II: T2NOMO	Sequential: total vaginectomy and pelvic lymphadenectomy; CR with EP; RT	CR	AWND	At least 12
Oliveira *et al.* in 2013 [8]	1	43	II: T2NOMO	Sequential: CT with EP; RT	CR	AWND	At least 5
Weberpals *et al.* in 2008 [11]	1	61	IV: TXN1M1	CT with EP	PR	Died	8
Coleman *et al.* in 2006 [12]	1	67	IV: T3N1M1	Sequential: RT; CT with EP	Recurrence with a metastatic lesion	AWD	At least 8
Petru *et al.* in 2004 [13]	1	50	II: T2NOM0	Sequential: anterior exenteration,pelvic lymphadenectomy; CT with EP and epirubicin	No description	Died	11
Zhanyong Bing *et al.* in 2004 [14]	3	74	IV: T3N1M1	Palliative CRT with CDDP and etoposide	PR	Died	4
		55	III: T2N1M0	Surgery: radical vaginovulvectomy and bilateral node dissection	Apparently CR but with distant failure	Died	4
		38	IV: T4NXM0	C-CR	Ongoing therapy	Alive	At least 5
Kaminski *et al.* in 2003 [15]	1	69	I: T1N0M0	C-CR with EP	PR	Died	13
Hayashi *et al.* in 2000 [17]	1	51	I: T1NXM0	CT with cyclophosphamide, pirarubicin and cisplatin	CR	AWND	At least 41
Elsaleh *et al.* in 2000 [18]	1	57	III: T3N0M0	C-CR with carboplatin and etoposide	CR	Died	14
Mirhashemi *et al.* in 1998 [19]	1	32	III: T3N0M0	Sequential: CT with EP; RT	CR	AWND	At least 6
Colleran *et al.* in 1997 [20]	1	59	II: T2N0M0	C-CR with EP	CP	Died	26
Miliauskas and Leong in 1992 [23]	1	78	III: TXN1M0	Surgery: modified right hemivaginovulvectomy and right side inguinal node dissection	CR	Died	10
Prasad *et al.* in 1992 [21]	1	34	II: T2N0M0	Sequential: vaginectomy and bilateral inguinal node dissection; CT with EP; RT	CR	Died	6

Table 1. Continued.

Literature	NO. Pa	Age, y	TNM stage	Primary therapy	Response	Outcome	Survival, mo
Joseph *et al.* in 1992 [22]	1	65	I: T1N0M0	Sequential: CT with vincristine, doxorubicin and cyclophosphamide; RT	CR	AWND	At least 24
Rusthoven and Daya in 1990 [24]	1	63	II: T2N0M0	Sequential: CT; RT	Local lesion progressed during CT	Died	Nearly 8
Chafe in 1989 [25]	2	78	II: T2N0M0	RT	CR	Died	15
		74	II: T2N0M0	RT	CR	Died	11
Hopkins *et al.* in 1989 [26]	3	41	II: T2N0M0	RT	No details about local response	Died	29
		68	IV: TXNXM1	RT and CT with adriamycin and cytoxan		Died	5
		73	IV: TXNXM1	CT with cisplatinum and dichloromethotrexate		Died	9
Fukushima *et al.* in 1986 [28]	1	32	II: T2N0M0	RT	CR	Died	12
Peters *et al.* in 1985 [29]	5	61 (mean)		No details	1 patient obtaining CR	Died	12 (mean)
Jain *et al.* in 2016 [6]	2			No clinical details			
Bhalodia *et al.* in 2011 [10]	1	50		No clinical details			
Ng *et al.* in 2003 [16]	1	70	IV: T4N0M0	CT	No description		
Ulrich *et al.* in 1986 [27]	1			No clinical details			
Scully *et al.* in 1984 [30]	1			No clinical details			

NO. Pa, number of patient; CT, chemotherapy; EP, etopside and cisplatin; RT, radiation; CRT, chemo-radiotherapy; C-CR, Concurrent chemo-radiation; PR, partial response; and CR, complete response; AWND, alive with no disease; AWD, alive with disease.

The stage was based on American Joint Committee on Cancer stage in 2002.

information. The clinical details of patients including 6 in stage I, 13 in stage II, 7 in stage III, and 7 in stage IV were showed in Table 1 (Ref. [1, 3–30]). The age of all patients ranges from 32 years to 81 years and the median is 59 years. The median survival time was 12 months, ranging from 4 months to 41 months. Four patients (1 in stage I and 3 in stage II) underwent surgery and postoperative chemo-radiotherapy. When therapy finished, all of them showed a clinical complete response (CR) and were alive without disease progression when reported. A patient in stage II received chemotherapy following surgery and two patients in stage III underwent surgery alone, all of them died within 1 year. Interestingly, the median survival time of the patients receiving radiation alone (1 in stage I and 4 in stage II) was 15 months and 80% of them achieved CR. Chemo-radiotherapy was administered to 14 patients (3 in stage I, 3 in stage II, 3 in stage III and 5 in stage IV). 7 of them achieved CR and 2 achieved partial response (PR). Disease progressed in 2 of them and outcome of 3 patients was unknown. The median survival time of patients treated by chemo-radiotherapy was 8 months. Three patients underwent chemotherapy alone and one of the them reported by Hayashi *et al.* [17] was alive for more than 41 months with no evidence of disease, and other of them die in 8 months and 9 months of diagnose, respectively.

5. Conclusions

Since radiation may be effective in local control, chemo-radiotherapy may be superior to chemotherapy alone in advanced cases, and surgery followed by chemo-radiotherapy may be also superior to surgery alone. Receiving chemotherapy and radiotherapy as soon as possible after surgery may improve prognosis.

Author contributions

JZ, YL and RY conceived and designed the review. JZ was involved in the collection and collation of references. YL collected and assembled the data presented in Table 1. JZ and YL wrote the manuscript. All authors approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of the First Affiliated Hospital of Chongqing Medical University approved the study. Approval number is 2020-655. All subjects gave their informed consent for inclusion before they participated in the study.

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Conflict of interest

The authors declare no conflict of interest.

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