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Case Report

Hormone replacement therapy for a young woman with cervical sarcomatoid squamous cell carcinoma

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Abstract: Cervical sarcomatoid squamous cell carcinoma (SSCC) is an extremely rare malignancy. We report the case of a young woman with cervical SSCC who experienced peri-menopausal syndrome following treatment, and present our evaluation of the considerations relating to hormone replacement therapy (HRT) in this case. A 24-year-old Chinese woman with SSCC underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Following surgery, she received radiation therapy, chemotherapy and lymphocyte immunotherapy; and developed severe menopausal symptoms. After assessing for the pathological type of carcinoma, hormone receptor status and disease stage, we performed HRT for this young woman. During the two years of follow-up, she remained cancer-free without post-menopausal symptoms. We conclude that HRT following surgery may be appropriate in certain young women with cervical sarcomatoid carcinoma to enhance their quality of life.

Keywords: Sarcomatoid squamous cell carcinoma, cervix, youth, hormone replacement treatment

Introduction

Surgical options in patients with malignant gynecological tumors primarily depend on their age, pathologic type, stage of disease, reproductive desires and tolerance for surgical procedures [1-3]. Young patients with certain gynecological tumors whose ovaries have been surgically removed or whose ovarian function has been badly damaged after chemo-radiotherapy may be candidates for hormone replacement therapy (HRT), depending on the pathological type of the neoplasm [4, 5]. To date, no reports have evaluated HRT as a component of post-surgical treatment in young women with a rare type of gynecological malignancy, cervical sarcomatoid squamous cell carcinoma (SSCC). In this report, we present a case of SSCC in a young woman who underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. In addition, she received radiation therapy (RT), chemotherapy and lymphocyte immunotherapy after the operation. This convalescent patient developed symptoms of post-menopause such as hot flushes and vaginal dryness. For this pathologic type, we aimed to determine whether HRT is contraindicated or beneficial.

Case

A 24-year-old Chinese woman, who is gravida 2 para 1 and had a cesarean section eight months ago, was admitted to our hospital with a 5-month history of contact bleeding. Her menstruation was regular before pregnancy and was restored in the second month postpartum. Her general physical examination was unremarkable, but cervical lesions were found and she had a prior history of retroperitoneal and intraspinal schwannoma, which had been surgically treated. On speculum examination (**Figure 1A**), the cervix appeared as a proliferative cauliflower-like mass, whose surface was covered with ulcerations. The mass was approximately 4×3×3 cm and had spread to the anterior fornix, but was limited to the upper 1/3 of the vagina. The posterior fornix was somewhat shallow. By abdominal-rectovaginal examination, the lesions had not spread to the parametrium. Ultrasonographic examination revealed a bulky cervix measuring 4.2×4.0×3.5 cm with a

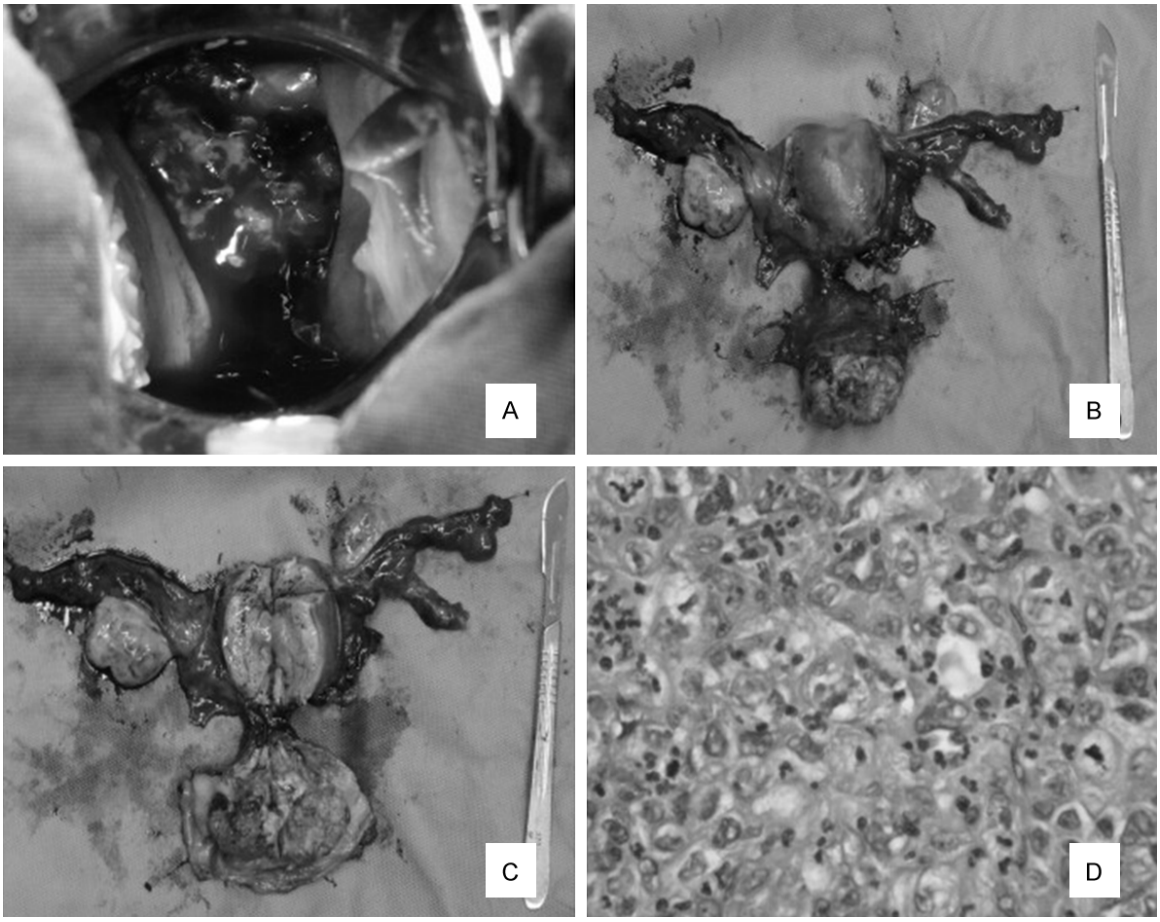

Figure 1. Sarcomatoid squamous cell carcinoma. A. On speculum examination, the cervix appeared as a proliferative cauliflower-like mass with an ulcerated surface. The mass was about 4 cm×3 cm×3 cm, limited to the upper 1/3 of the vagina, with a slightly shallow posterior fornix; B. The operative findings. A 4.5 cm×4.3 cm×3.8 cm exophytic protruded cervical tumor; C. Cutaway view of the uterus and cervix. The tumor involved the deep layers of the cervix; D. Under microscopic examination, the cells were arranged in various forms, with hypercellularity and nuclear atypia (HE×40).

slightly heterogeneous echotexture. Her chest X-ray was normal. The cervical mass was biopsied, and results indicated the presence of malignant spindle cells. The hospital pathologist examined the pathological sections from the woman's two previous operations and confirmed that her previous schwannomas were benign, which excluded the possibility of metastasis. According to the International Federation of Gynecology and Obstetrics staging system of 2009, a clinical diagnosis was made of stage II A2 cancer. Transabdominal radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy was performed. Operative findings revealed a 4.5×4.3×3.8 cm exophytic protruded cervical tumor involving the deep layers of the cervix (**Figure 1B** and **1C**) and a significantly enlarged left common iliac lymph node. This enlarged lymph node revealed reactive hyperplasia by intraoperative frozen-section pathological examination. Histopathological examination confirmed the diagnosis of cervical SSCC (**Figure 1D**), and indicated that these tumor cells were poorly differentiated with local sarcomatoid carcinoma components (approximately 35%) and that the lesion had invaded into the deep muscular layer of the cervix without spreading into the uterine body or pelvic lymph nodes. Furthermore, surgical resection margins were free of tumor cells. Subsequent immunohistochemical staining revealed that the sarcomatous element was positive for cytokeratin (CK, **Figure 2A**), epithelial membrane antigen (EMA, partial; **Figure 2B**), P16 (**Figure 2C**), CD10 (partial, **Figure 2D**), P63 (**Figure 3A**), vimentin (Vim, **Figure 3B**) and

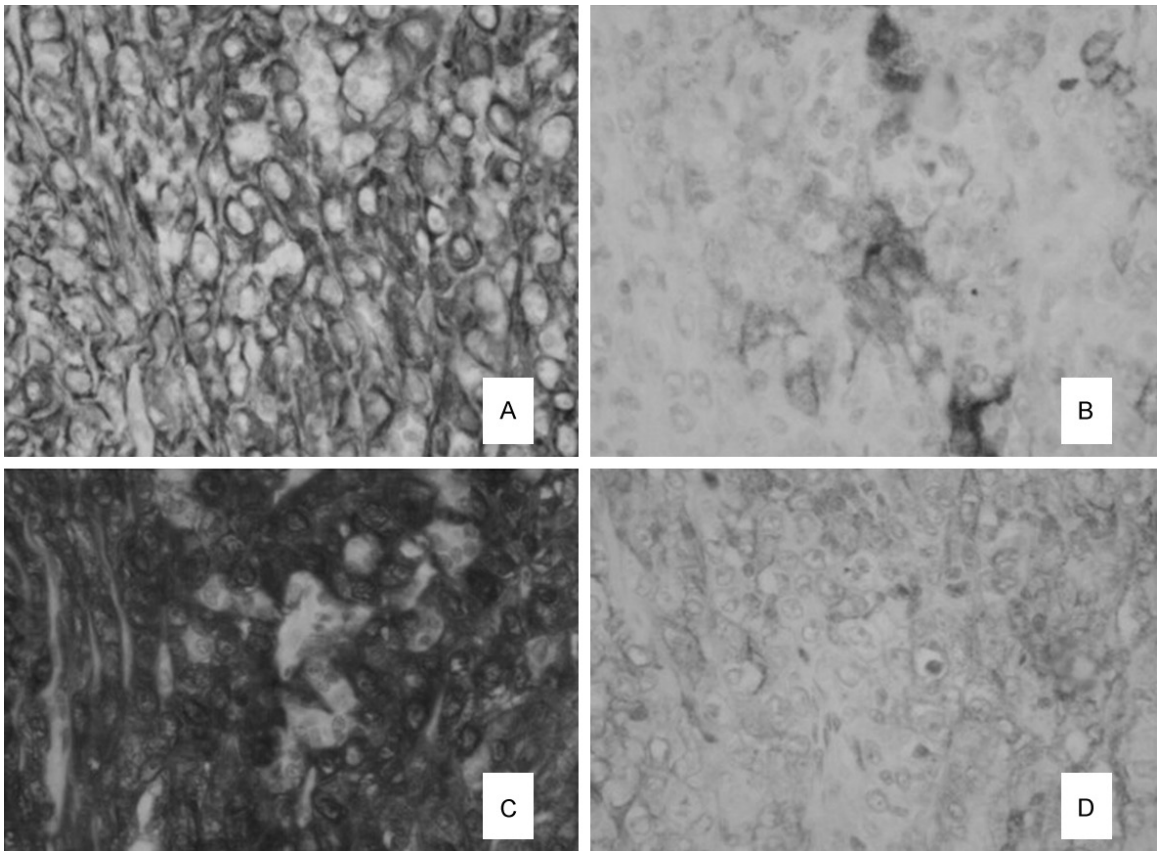

Figure 2. Immunohistochemical study. A. CK 40x; B. EMA 40x; C. P16 40x; D. CD10 40x. Immunohistochemical staining for CK was positive in the cytomembrane, and for P16 was positive in the cytoplasm, both diffusely. Immunohistochemical staining for EMA and CD10 were both focally positive in the cytomembrane and cytoplasm.

antigen ki67 (60%, **Figure 3C**); while it was negative for the following: carbohydrate antigen-125 (CA-125), progesterone receptor (PR), estrogen receptor (ER, **Figure 3D**), smooth muscle actin (SMA), desmin (Des), mucin 5AC (Muc5AC), Muc-2 glycoprotein (Muc2) and human papilloma virus (HPV). The patient underwent chemotherapy with taxol (175 mg/m^2) and carboplatin (268 mg/m^2) for two cycles after surgery, following which she received external beam radiation with 25 applications of 2,000 cGy (a total dose of 50 Gy) of 10-MV X-ray. Subsequently, she received three cycles of alternating treatments of chemotherapy (taxol, 175 mg/m^2 for one day; and ifosfamide, 100 mg/m^2 for four days) and autoimmune cell therapy. The autoimmune cell therapy involved activating and amplifying the patient's own cytokine-induced killer cells *in vitro*, and slowly returning them back to the patient over a period of 15 days, to enhance the patient's immune function and anti-tumor potential.

Beginning one week after surgery, the patient exhibited symptoms of mild hot flushes, night sweats andagrypnia. At that time, she continued to receive adjuvant therapy, but she did not see a doctor regarding these symptoms. More than two months later, after the adjuvant therapy was completed, she presented at an outpatient clinic with severe peri-menopausal symptoms (according to the patient, these included hot flushes a dozen times a day, night sweats three or four times per night, severe agrypnia, hot temper and vaginal dryness). After use of transcutaneous estrogen estradiol hemihydrate (Merck KGaA, Germany) for one week, her symptoms of hot temper andagrypnia were in complete remission, and her hot flushes and night sweats showed a significant clinical response. After the second week, all her constitutional symptoms disappeared, except for vaginal dryness. However, local vaginal estrogen creams (Promestriene or Colpotrophine), which act locally and rarely enter the blood circula-

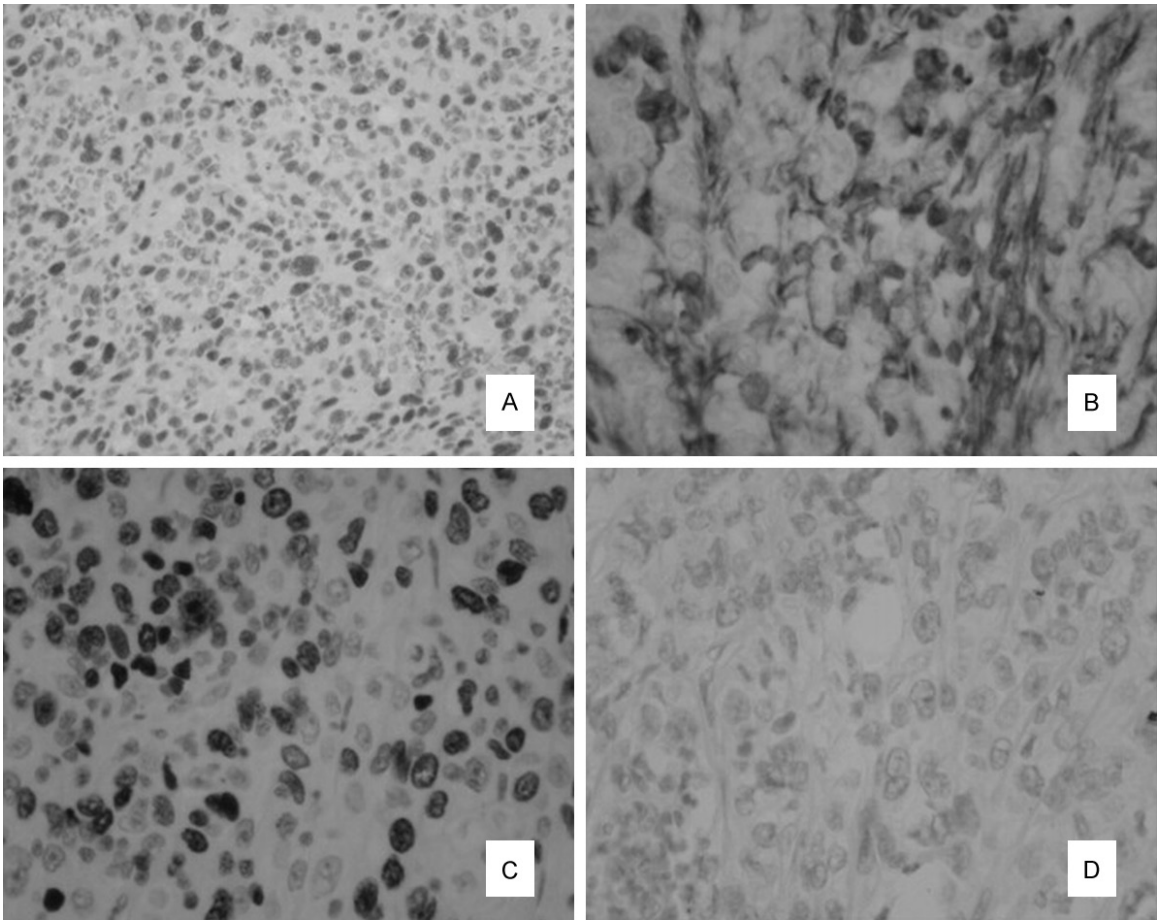

Figure 3. Immunohistochemical study. A. P63 20x; B. Vim 40x; C. ki67 40x; D. Estrogen receptor (ER) 20x. Immunohistochemical analysis for P63 showed positive nuclear staining and for Vim showed positive cytoplasmic staining, both diffusely. Immunohistochemical analysis for ki67 showed positive nuclear staining (67% focally), and for ER, no staining (negative).

tion, improved this symptom in approximately ten days. During close follow-up for two years, the patient has remained tumor-free without post-menopausal symptoms, with an enhanced quality of life due to HRT.

Discussion

Cervical cancer is the third most common cancer in females, which causes severe morbidity and mortality in developing countries [3, 6]. The incidence of cervical cancer is related to age and pregnancy. In women who have been pregnant, the mean age at onset of carcinoma *in situ* and invasive cancer is younger, compared to women who have never been pregnant [7-9]. The most common histopathology in cervical cancer is squamous cell carcinoma, which accounts for over 90% of all cervical cancers. Adenocarcinoma constitutes approximately 2%-4%, and other histological types account for the rest [10]. SSCC is a rare type of malignant tumor, which can occur in any organ. SSCC is composed both of a squamous cell carcinoma element and a spindle cell sarcoma element. The diagnosis of sarcomatoid carcinoma is based on histologic, immunohistochemical and ultrastructural characteristics [10]. In the case described herein, according to histopathological and immunohistochemical findings, cervical sarcomatoid cells were positive for CK, P16, CD10, P63 and ki67. This indicate that the sarcomatoid element was derived from the squamous cell carcinoma (SCC) element [11]. However, sarcomatoid cells were also strongly positive for Vim, which is specifically expressed in sarcomatoid carcinoma, and is not found in squamous cell carcinoma (SCC) [11, 12]. Tumors stained negatively for Des, Muc5AC and Muc2; which were ruled out as a malignant

tumor of gastrointestinal tract origin. The tumor was also negative for CA-125, which excluded cancer derived from the ovary. Furthermore, given her prior history of schwannoglioma, we examined the archived pathological sections and excluded the possibility of metastasis. Together, these findings confirmed the diagnosis of cervical SSCC.

The prognosis of cervical sarcomatoid carcinoma tends to be worse than that of squamous carcinoma. The reported survival ranges from six months to 14 years [11, 13]. The biological behavior of SSCC is very aggressive [11] and RT remains the main modality of treatment. Pelvic radiotherapy (PRT) after surgery is considered in cases of positive surgical resection margins when the parametrium is involved, or when lymph nodes are involved [13, 14]. RT has been shown to decrease local recurrence and reduce mortality by approximately 75%. In spite of this, the patterns of recurrence are variable and appear to be unrelated to the initial treatment. For the patient described herein, sarcomatoid carcinoma was found in more than one third of the entire tumor, and RT was subsequently initiated. Presently, after two years of follow-up, is well with no recurrence or metastasis occurred.

When an ovary is removed on account of malignancy, or its function is lost after radiotherapy, estrogen levels in the body severely decrease. Peri-menopausal symptoms such as hot flushes, insomnia, osteoporosis, coronary heart disease and so on occur in most of these patients, which seriously affect their physical and mental health. In general, ovariectomy for iatrogenic factors lead to an acute onset of menopausal symptoms, which are more intense and severe than that of natural menopause [5, 7, 15]. HRT has been proven to be very effective in alleviating these symptoms. Thus, it can have a significant impact on a woman's quality of life after bilateral-oophorectomy [5, 15, 16]. However, the use of hormone therapy to treat menopausal symptoms in women who are gynecological cancer survivors continues to be controversial [5]; in which major concerns include the fear of recurrence, risk of breast cancer, venous thromboembolic disease and other conditions associated with long-term hormone therapy use [15].

Whether HRT is used or not should be based on tumor type and grade, hormone receptor status and disease stage [17]. There are currently no relevant reports on HRT use in cervical sarcomatoid carcinoma, which makes this case significant.

As a result of the local effects of radiation and bilateral salpingo-oophorectomy, vaginal atrophy, dyspareunia, vaginal stenosis or even complete occlusions may occur; and for this young patient, vaginal dryness and dyspareunia were serious. For her local symptoms, we suggested local estrogen administration, which was very effective, as well as safe and practical. For her systemic symptoms, we suggested the use of HRT to improve her overall quality of life. Our rationales are as follows. (1) Progesterone and estrogen work by binding specifically to their intracellular steroid receptors [18]. For this patient, her sarcomatoid carcinoma cells were negative both for PR and ER. Therefore, this sarcomatoid carcinoma was not a hormone-dependent tumor. (2) Cervical SCC is not considered to be an estrogen-responsive disease [5, 7, 19], although estrogen receptors may be present in squamous cell cancer tissues. An association between the use of hormonal therapy and cervical carcinoma has never been proven [5, 20]. (3) In HPV-positive women, hormone therapy acts as a co-factor together with oncogenic HPV to promote cell proliferation; thus, estrogen leads to increased cervical cancer risk [7, 21]. However, this patient's tumor was negative for HPV.

In women without an intact uterus, estrogen therapy alone can be used to treat post-menopausal symptoms, without the need for progesterone to protect the endometrium [4, 22]. As was done with this patient, local vaginal estrogen-like creams or pessaries may be applied to reduce radiation-induced local side effects [7, 15], since there is no clear evidence that this causes a worse prognosis [4, 22]. With respect to systemic symptoms of low estrogen, either oral or transdermal estrogen therapycan be used. For vasomotor symptoms, the use of progestin therapy and selective serotonin reuptake inhibitors are the only agents that have been shown to be effective [17].

Surgical removal of the ovaries or radiation and chemotherapy-induced ovarian failure combined with primary malignancies often leads to significant physical and mental distress among patients. The main goals of clinical treatment of

malignant tumors should not only to reduce mortality and recurrence rates, but also to consider the quality of life of patients as an important indicator of its therapeutic effect. The effectiveness of HRT in improving quality of life is indisputable, but for cervical SSCC, no literature reports had previously evaluated its safety.

Conclusion

In the cervical SSCC case reported in this review, the patient was treated with HRT and followed up for more than two years. Her clinical symptoms, as assessed by ultrasound, carbohydrate antigen detection, chest X-ray, Thinprep cytology test (TCT) and other tests, indicated no signs of tumor recurrence. Furthermore, the patient's physical and mental condition remains good, with no reports of discomfort. Thus, in evaluating treatment options in subsequent cases of cervical SSCC, HRT therapy should be strongly considered, with successful treatment of this patient as a reference. However, the pathological type of the tumor still needs to be taken into account, as we continue to explore the safety and effectiveness of HRT.

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Disclosure of conflict of interest

None.

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