A Case of Mixed Small and Large Cell Neuroendocrine Carcinoma of the Uterine Cervix

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A rare case of mixed carcinoma of the cervix is reported, composed of a small and large cell neuroendocrine carcinoma. Neuroendocrine cervical carcinomas are very rare and aggressive. The prognosis is very poor despite multimodal treatment. Earlier reports have shown that the majority of patients present with advanced stage disease, have lymph node metastasis, and are at a high risk for recurrence and disease progression. In this study, we report the case of a 26-year-old woman with composite small and large cell neuroendocrine carcinoma of the cervix. A woman presented with vaginal bleed since 2 months of presentation. Gynecologic examination revealed cervical enlargement, and punch biopsy of the cervical lesion was performed. The biopsy was disclosed a large cell neuroendocrine carcinoma. The patient underwent a radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection. The final histopathologic findings are mixed small and large cell neuroendocrine carcinoma of cervix.

Keywords: Uterine cervical neoplasms; Neuroendocrine carcinoma; Small cell carcinoma cervix; Large cell neuroendocrine carcinoma

INTRODUCTION

Neuroendocrine carcinoma of cervix is a rare and highly aggressive disease, mainly developing at the expense of the respiratory and of the digestive tract. In 1972, Albores-Saavedra first recognized the disease [1]. Small cell neuroendocrine carcinoma of the cervix represents less than 5% of cervical cancer [2]. The incidence of large cell neuroendocrine carcinoma (LCNEC) has been reported to be 0.087% to 0.6% of cervical carcinomas [3]. Due to the rarity of disease, there are much difficulties in drawing conclusion on overall management. Furthermore, the prognosis is highly poor due to early distant hematogenous metastasis. Despite multimodality regimens, the prognosis of these carcinomas remains poor. In the case of neuroendocrine carcinoma of cervix, as reported, the 2-year and 5-year disease-survival rates were 54.8% and 31.5% [4]. We present our experience with a patient diagnosed with mixed small and large neuroendocrine carcinoma of the cervix.

CASE REPORT

A 26-year-old woman (2-0-4-2) had suffered vaginal bleeding for 2 months. Physical examination revealed no abnormal findings, and gynecological examination showed protruded exocervical mass. Her blood test showed the following results: hemoglobin 12.3 g/dL, white blood cell 7,020/µL, and platelet 218,000/µL. Liver function tests, renal function tests, and coagulation profile were all normal. The level of tumor marker (squamous cell carcinoma, carcinoembryonic antigen, cancer antigen 125, carbohydrate antigen 19-9, alphafetoprotein, β-human chorionic gonadotropin) was normal. She was positive for high-risk human papillomavirus (HPV) 18.

The pelvic magnetic resonance imaging showed about 3.5 cm sized mass lesion in or around uterine cervix with faint enhancement, which suggested cervical cancer confined within uterus (stage I or IIA) (Fig. 1). In positron emission tomography-computed tomography, there were enlarged lymph nodes in both external ili-
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ac area, which presents metastatic lymphadenopathies. The result of cervical punch biopsy was a LCNEC. Immunohistochemically, CD56, synaptophysin, and chromogranin A were positive.

She underwent radical hysterectomy with bilateral salpingo-oophorectomy with pelvic lymph node dissection. During operation, the yellowish-pale appearance 4 × 4 cm sized cancerous mass was found confined within uterus. Grossly, invasion into parametrium or vagina was not found. The left external iliac and both obturator lymph nodes were enlarged on palpation.

The pathological tumor size was estimated 4.5 × 4.0 × 2.7 cm. Invasion was 2.7 cm in depth. The metastasis of lymph node and venous invasion was not identified although lymph nodes were enlarged on palpation during operation. Histologically, the tumor had a mixed cell pattern mixed small cell and LCNEC (small cell, 90%; large cell, 10%) (Fig. 2). Most part of the cancer was composed of small, dark cells in a nested pattern. Small part of the cancer was composed of large cells which had an enlarged pale, large nucleus (Fig. 2B). There were many enlarged pleomorphic cells in a nested pattern and frequent apoptotic bodies. On immunohistochemical staining, CD56 and chromogranin A were positive (Fig. 2C, D).

The patient was recommended to receive chemotherapy. She underwent 6 times of concurrent chemoradiation therapy (cisplatin based CCRT). After CCRT, the patient has been without evidence of the disease 18 months later.

**DISCUSSION**

Neuroendocrine carcinoma of the uterine cervix is a rare disease. Neuroendocrine tumors of the uterine cervix are classified under 4 categories according to histology: (typical) carcinoid, atypical carcinoid, LCNEC, and small cell carcinoma [5].

Small cell carcinoma of the uterine cervix (SCCC) is a rare disorder taking up only 0.5% to 5% of the types of cervical cancer [6]. One of the causes SCCC is HPV infection, and in particular, HPV type 18 is closely associated [7]. Clinically, SCCC has similar characteristics with small cell lung carcinoma [8]. The light microscopy and immunohistochemical staining are used for diagnosis of the disease and the tumor cells behave similarly to the lung [8]. When immunohistochemically stained, they are positive for general neuroendocrine markers including synaptophysin, chromogranin A, neuron-specific enolase, and CD56 [9]. SCCC has an aggressive nature with poor prognosis due to early distant hematogenous metastasis. Even in early stage, SCCC tends to metastasizes to distant organ like bone, brain, liver, and bone marrows. In addition, the tumors are remarkably resistant to conventional treatment modalities. In a retrospective study of 21 patients with SCCC, overall survival rates were 43% and 29% at 2 and 5 years, respectively. The 10-year survival was 55% in small cell compared with 76% and 88% in adenocarcinoma and squamous cell patients, respectively, of those with stage IBI disease [10]. Given the aggressive nature of this tumor, the use of multimodality treatment with chemotherapy even in early-stage disease should be considered [11]. The treatment of SCCC is a radical hysterectomy, pelvic lymph node dissection, and para-aortic lymph node dissection, and adjuvant chemotherapy and radiation therapy are added after surgery. SCCC is highly responsive to multiple chemotherapeutic drugs, and chemotherapy dramatically prolonged survival compared to best supportive care [8].

LCNEC is characterized by early tumor recurrence despite radical surgery, radiotherapy and chemotherapy. These tumors are highly aggressive neoplasms. LCNEC are more rare and aggressive than SCCC. The incidence of LCNEC has been reported to be 0.087% to 0.6% of cervical carcinomas in recent literature [3,12]. The diagnosis of LCNEC must be confirmed by an argyrophilic reaction or immunopositive results for chromogranin or synaptophysin [5,13]. However, positive rates of LCNEC were 87% for chromogranin, 56% for synaptophysin, and 88% for at least one of chromogranin, synaptophysin, CD56, or neuron-specific enolase [14]. The presence of HPV has been demonstrated in most reported cases of LCNEC, ranging
from 53% to 100% [15], and associated with HPV16 and HPV18. Consequently, currently available HPV vaccines may enable us to eliminate this tumor. In recent multivariate analysis of 62 patients with large cell neuroendocrine cervical cancer, earlier FIGO (Federation of Gynecology and Obstetrics) stage and chemotherapy at any point during initial treatment were associated with improved survival [16]. Among of several regimens, both platinum and platinum and etoposide were associated with improved survival versus other drugs [16]. Krivak et al. [17] and Li et al. [18] reached a similar conclusion that chemotherapy was an integral part of multimodality therapy secondary to the propensity for distant hematogenous metastasis.

Kim et al. [19] emphasized uterine cervical biopsy is important and reliable method to differentiate between malignant and benign mass. In the case of our patient, we were done cervical punch biopsy, the tumor was composed of both small cell neuroendocrine carcinoma (90%) and LCNEC (10%). So, the patient was treated by cisplatin based concurrent chemoradiotherapy. Until now she does not have any evidence of disease. Maybe it suggests that intensive multimodal therapy including chemotherapy is a crucial part of treatment in neuroendocrine cervical carcinoma once again.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.
REFERENCES